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Review

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Long-term survival of robotic lobectomy for non-small cell lung cancer: a literature review

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Abstract

Even though robotic-assisted surgery is increasingly used for resection of non-small cell lung cancer (NSCLC), data on long-term oncologic outcomes of robotic surgery are still not well defined. The primary endpoint of this review is to analyse the long-term results of robotic lobectomy in NSCLC patients. A systematic research was performed using the PubMed database. Articles published from January 2008 to January 2019 were included. We excluded studies that did not provide results for the long-term outcomes of robotic lobectomy, studies that had fewer than 50 cases and ones that focused on results of sub-lobar resections. Therefore, ten eligible studies were included in this analysis. In total, 2873 patients, with a mean age ranging between 66 and 68 years, who underwent robotic lobectomy for NSCLC, were analysed. Most patients (81%) had early-stage disease. The five-year overall survival for stage I disease fluctuated between 77% and 100%. The five-year disease-free survival was reported to be near 73%. We can conclude that robotic assisted lobectomy is an effective minimally-invasive procedure for lung resection. The current literature shows that robotic lobectomy is associated with long-term survival and lasting disease-free survival, equivalent to those reached by video-assisted thoracic surgery and open approach.

Keywords: Non-small cell lung cancer, robotic surgery, robotic lobectomy, long-term outcome, minimally invasive surgery

INTRODUCTION

Surgical resection of non-small-cell lung cancer (NSCLC) is the preferred local treatment modality for operable disease and lobectomy remains the gold standard treatment in early-stage lung cancer^[1]. Thanks



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to the technical and technological improvements achieved during the decades, the surgical approach has moved from open procedures to minimally invasive surgery (MIS). MIS [including video-assisted thoracic surgery (VATS) and robot-assisted surgery] has become the preferred approach in patients with no contraindications (anatomic or surgical), given that the less invasive approach does not compromise the oncologic cancer outcomes and is associated with better short-term results compared to thoracotomy^[2].

Regardless of the approach, the oncologic principles remain unchanged: the achievement of negative margins (R0 resection) and a systematic lymph node dissection; the open approach for lobectomy remains the cornerstone with which the results of the other techniques are compared.

Recent data have reported an important increase in VATS and robotic lobectomy versus open procedures and several studies have shown that MIS lobectomy results in comparable oncologic outcomes to those of open approach^[3,4]. However, Level 1 evidence does not exist and data on long-term outcomes for NSCLC patients treated with robotic approach are still lacking^[5].

The aim of this review is to analyse the literature concerning the long-term survival of robotic lung lobectomy.

METHODS

A literature review was conducted by searching PubMed in July 2019, using the search terms: (“lung cancer” OR “lung tumour” OR “lung neoplasm” OR “NSCLC”) AND (“robotic” OR “robot assisted” OR “da Vinci” OR “daVinci”) AND [“analysis, survival” (MESH TERMS)].

Inclusion criteria were: (1) the paper described robotic-assisted lobectomy; and (2) the study was a randomised controlled trial, meta-analysis or single centre/multicentre database study recording on robotic lobectomy.

Exclusion criteria were: (1) the study did not provide results for the long-term outcomes of robotic lobectomy; (2) the study focused on results of sub-lobar resections; and (3) the study included fewer than 50 cases.

After language restriction (English), applying inclusion and exclusion criteria and eliminating duplicate papers, ten studies were selected for this analysis, all reporting robotic lung lobectomy for NSCLC [Figure 1].

RESULTS

Six retrospective, observational single centre studies, three retrospective multicentre studies and one prospective cohort study published between 2008 and January 2019 were included in this analysis [Table 1]. In total, 2873 patients, with a mean age ranging between 66 and 68 years, who underwent robotic lobectomy for NSCLC, were analysed.

The majority of patients (81%) had early-stage disease [1892 stage I (66%), 443 stage II (15%)] and only a few of them had advanced or metastatic disease [507 stage III (18%), 31 stage IV (1%)].

Short-term outcomes

The mean length of stay reported was 4.5 days (ranging between 3 and 8 days), the mean conversion rate was 8.4% (ranging between 0% and 9.8%) and the mean post-operative 30-day mortality was 0.25% (ranging between 0% and 4.9%).

The mean rates of reported overall complications and major complications were 25.4% (ranging between 9.52% and 66.4%) and 5.85% (ranging between 2.4% and 10.3%), respectively [Table 1].

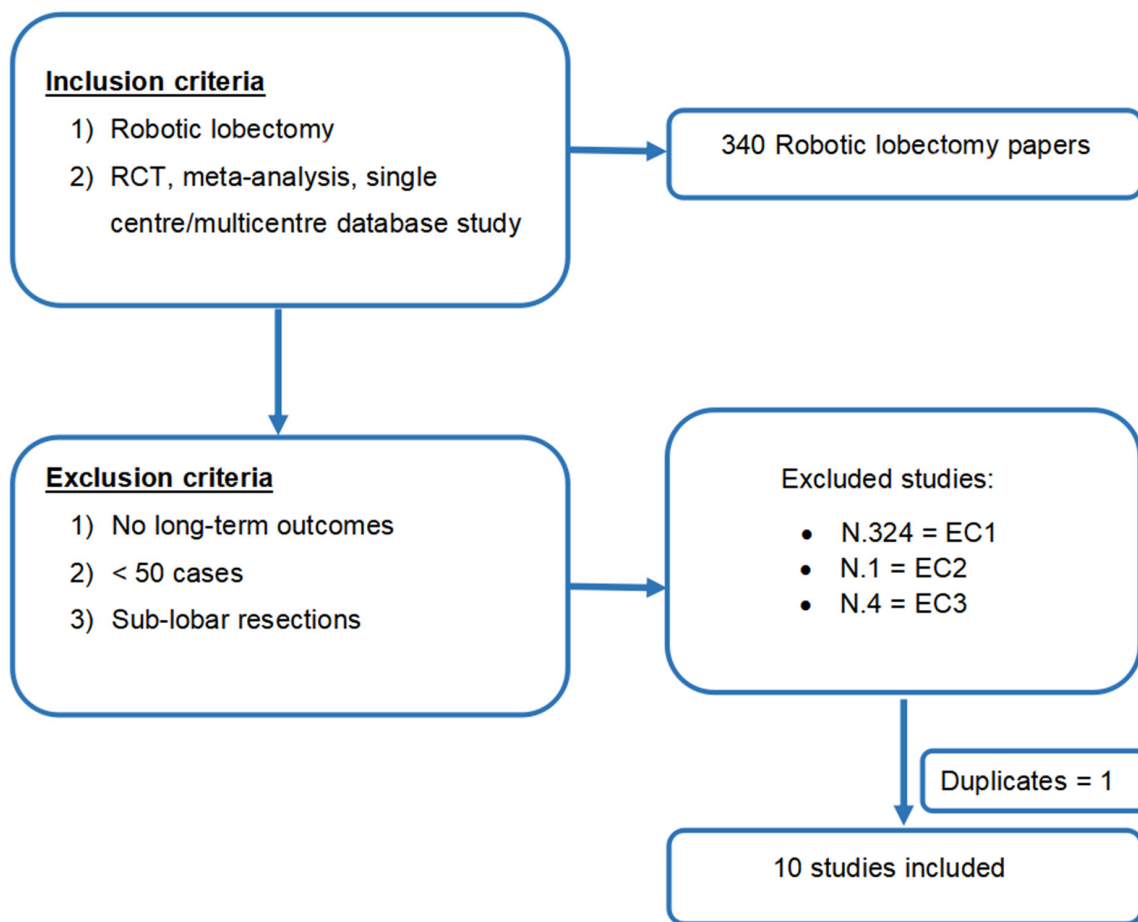


Figure 1. We present graphically our searching strategy. RCT: randomized control trial

Mid- and long-term outcomes

The mid- and long-term outcomes of 2850 patients were analysed, with a survival time analysis ranging between two years and five years. Seven studies showed the survival of patients who underwent robotic surgery in a single centre with a follow-up ranging between 13.3 and 40.3 months. The studies were inhomogeneous for survival time analysis (two-, three- or five-year results) and patients' stage (only stage I analysis or multiple stage data) [Table 2].

Toosi *et al.*^[6] analysed 249 patients who underwent robotic lobectomy and showed a mean operative-time, conversion rate and rates of perioperative outcomes comparable to those of VATS and open surgery. The primary endpoint of this study was the evaluation of the effectiveness of lymphadenectomy (LN) by robotic approach and the authors revealed that LN staging with robotic surgery was comparable to or better than that obtained with conventional VATS and open approach. Moreover, the authors showed an overall survival (OS) comparable with that described in the literature, but the survival analysis was limited by the short mean follow-up time (18 months).

The aim of the study published by Yang *et al.*^[7] was to compare the long-term outcomes [OS and disease-free survival (DFS)] of three cohorts (robotic, VATS and open) of clinical stage I NSCLC patients matched by propensity score. The authors stated that MIS lobectomy for clinical stage I NSCLC guarantees comparable long-term survival as thoracotomy and was associated with shorter hospitalisation. The five-year OS and DFS for the robotic group were 77.6% and 72.7%, respectively, and 13.5% (25/184) patients experimented recurrences.

Table 1. Short-term outcome of NSCLC treated by Robotic approach

Ref.	Year	Number of patients	Type of study	Conversion rate	n of resected lymph nodes or n of station	Upstaging	Hospital stay (days)	Complications	Mortality	
									30 days	90 days
Toosi <i>et al.</i> ^[6]	2016	249	Retrospective single centre	22 (8.8%)	13.9 ± 0.4 nodes (range 1-37)	26.9%	5	90 (36.1%)	6 (2.4%)	
Veronesi <i>et al.</i> ^[14]	2018	210	Retrospective multicentre	22 (9.9%)	15.4 nodes (SD 7.9)	NA	5.3	148 (66.4%) Grade III-IV 23 (10.3%)	4/209 (1.9%)	8/198 (4%)
Yang <i>et al.</i> ^[7]	2017	172	Prospective single centre	16 (9%)	5 stations (range 0-8)	NA	4	51 (29.7%)	0	
Lee <i>et al.</i> ^[8]	2015	53	Retrospective single centre	1 (1.9%)	17 nodes (range 4-40)	13.2%	3	6 (9.52%)	0	
Park <i>et al.</i> ^[13]	2011	325	Retrospective multicentre	27 (8%)	5 stations (range 2-8)	24%	5	82 (25.2%) Major 12 (3.7%)	1 (0.3%)	
Gharagozloo <i>et al.</i> ^[9]	2008	54	Retrospective single centre	0	NA	16%	4	14 (22%)	3 (4.9%)	
Cheufou <i>et al.</i> ^[10]	2019	64	Retrospective single centre	6 (9.4%)	13.9 nodes (SD 6.5)	12.9%	8.3/7.9		0%	
Cerfolio <i>et al.</i> ^[15]	2018	1321	Retrospective multicentre	116 (9%)	19 nodes (range 11-42)	NA	3	24% Major 8%	0.2%	0.5%
Casiraghi <i>et al.</i> ^[11]	2019	307	Retrospective single centre	22 (6.5%)	15 nodes (range 1-55)	17.6%	5	87 (25.7%) Major 8 (2.4%)	0	0.3%
Zirafa <i>et al.</i> ^[12]	2019	212	Retrospective single centre	9 (4.2%)	17.4 nodes (range 7-37)	NA	3.6	54 (25.5%)	1 (0.4%)	

NSCLC: non-small-cell lung cancer; NA: not assessed

Another comparative study was the one by Lee *et al.*^[8] The authors retrospectively analysed clinically node negative NSCLC patients who underwent VATS ($n = 158$) or robotic ($n = 53$) lobectomy showing a similar rate of nodal upstaging and similar DFS and OS between the two groups. In the robotic cohort with a mean follow-up of 13.3 months, the OS and DFS were 95% and 93%, respectively. They reported three (5.6%) cancer recurrences (all distant). One of the first studies which reported long-term outcomes of robotic surgery was published in 2008. With a follow-up of 28 months, Gharagozloo *et al.*^[9] reported an OS of 100% and a DFS of 93% in a cohort of stage I and II NSCLC patients. No recurrences occurred.

A recent study conducted by Cheufou *et al.*^[10] reported data on 64 patients who underwent robotic lobectomy for lung cancer. Their results showed a two-year survival rate of 83% with a rate of nodal upstaging of 12.9%.

Analyses of larger groups of patients were performed by Casiraghi *et al.*^[11] and Zirafa *et al.*^[12] Casiraghi *et al.*^[11] reported data on 307 lobectomies, 29 segmentectomies and 3 pneumonectomies performed by robotic approach in NSCLC patients (stage IA-IIIa). The five-year OS of the lobectomy cohort was 89.1% with a DFS of 72.8%. There were 58 recurrences: 16 local (ipsilateral to the operated chest), 27 regional (contralateral) and 15 distant.

Zirafa *et al.*^[12] analysed 212 patients who underwent robotic lobectomy ($n = 211$) and bilobectomy ($n = 1$) for NSCLC (stages IA-IV). With a mean follow-up of 40.3 months, they reported a five-year survival of 98.5% (stage I), 93.7% (stage II), 73.1% (stage III) and 0% (stage IV). The overall DFS was 66.3 months. Overall, 12.7% of loco-regional relapse and 10.9% of distant recurrence were observed.

Three retrospective multicentre studies were also included in this review. The first was conducted by Park and examined data on 325 patients who underwent robotic lobectomies in three high volume centres: 123 patients in New York, 82 in Milan and 120 in Pisa. The majority of the patients (76%, 248/325) were pathologic stage I (176 stage IA and 72 stage IB). Overall one- and five-year survival for the group was 98% and 80%, respectively. Twenty-five patients died of their disease. At a mean follow-up of 27 months, the

Table 2. Mid- and Long-term outcomes of NSCLC treated by Robotic approach

Ref.	Year	Number of patients	Type of study	Intervention	Follow-up (months)	Survival time analysis	Overall survival				DFS
							pStage I	pStage II	pStage III	pStage IV	
Toosi <i>et al.</i> ^[6]	2016	249	Retrospective single centre	Lobectomy	18	3-year	75%	73%	44%	0%	/
Veronesi <i>et al.</i> ^[14]	2018	210	Retrospective multicentre	Lobectomy	18	3-year	/	/	61.2%	/	37.7%
Yang <i>et al.</i> ^[14]	2017	172	Prospective single centre	Lobectomy	39.8	5-year	77.6%	/	/	/	72.7%
Lee <i>et al.</i> ^[8]	2015	53	Retrospective single centre	Lobectomy	13.3	2-year		95%		/	93%
Park <i>et al.</i> ^[13]	2011	325	Retrospective multicentre	Lobectomy	27	3-year	97% (IA), 88% (IB)	72%	43%	/	90%
Gharagozloo <i>et al.</i> ^[9]	2008	54	Retrospective single centre	Lobectomy	28	2-year	100%	100%	/	/	93%
Cheufou <i>et al.</i> ^[10]	2018	64	Retrospective single centre	Lobectomy	/	2-year		83%		/	/
Cerfolio <i>et al.</i> ^[15]	2018	1321	Retrospective multicentre	Lobectomy	30	5-year	83% (IA), 77% (IB)	68% (IIA), 70% (IIB)	62% (IIIA), 31% (IIIB)	54%	Mean DFS: 16 months
Casiraghi <i>et al.</i> ^[11]	2019	307	Retrospective single centre	Lobectomy	28.8	5-year		89.1%		/	72.8%
Zirafa <i>et al.</i> ^[12]	2019	212	Retrospective single centre	211 Lobectomy 1 Bilobectomy	40.3	5-year	98.5%	93.7%	73.1%	0%	Mean DFS: 66.3 months

DFS: disease free survival; NSCLC: non-small-cell lung cancer

recurrence rate was 10% (32/325). Most recurrences (72%) were distant (17 distant only; 6 locoregional + distant), and 28% (9/32) were locoregional only^[13].

The retrospective multicentre (seven centres) study led by Veronesi *et al.*^[14] analysed 223 patients with NSCLC or carcinoid, with pathological (post-surgical) N2 disease (Stage IIIA) treated by robot assisted resection with curative intent, before or after chemotherapy or chemoradiation therapy. The study included 34 patients who underwent resection after induction therapies. With a mean follow-up of 18 months, mean survival for the 210 NSCLC patients (13 carcinoids) was 51 months, with three-year OS estimated at 61.2%. Twenty-five per cent of patients (56 cases) had distant relapse and 16.6% had local or lung recurrence.

Cerfolio *et al.*^[15] reported the largest series of robotic lobectomy for NSCLC in four high volume centres. The authors analysed short- and long-term outcomes of 1339 and 1321 patients, respectively. Approximately 50% of patients had stage IA disease (672/1339). With a mean follow-up of 30 months (ranging between 1 and 154 months), the five-year stage-specific survival was: 83% for stage IA, 77% for stage IB, 68% for stage IIA, 70% for IIB, 62% for stage IIIA and 31% for stage IIIB. The recurrence rate was 15% (distant) and 3% (local).

CONCLUSIONS

Robotic approach for lobectomy is one of the newest evolutions in MIS for NSCLC; however, long-term data on its oncologic efficacy are still limited. For this purpose, in this review, we have analysed ten studies, both monocentric and multicentric, to examine oncologic outcomes of patients who underwent robotic lobectomy.

Concerning short-term results, the robotic surgery has shown several promising results such as conversion rates to thoracotomy, transfusions rate, length of stay and readmission rates compared with VATS. A propensity-matched analysis conducted by Oh *et al.*^[5] comparing open lobectomy and robotic lobectomy showed a lower postoperative complication rate, lower mortality rate and shorter hospital stay in the robotic cohort.

The conversion rate exposed in the present review ranges between 0% and 9.8%, comparable to that reported in the literature and lower than that of VATS^[16-18]. Only one study reported a higher conversion

Table 3. Stage specific overall survival according to the eighth edition of TNM

Stage	Two-year survival	Five-year survival
IA1	97%	92%
IA2	94%	83%
IA3	90%	77%
IB	87%	68%
IIA	79%	60%
IIB	72%	53%
IIIA	55%	36%
IIIB	44%	26%
IIIC	24%	13%
IVA	23%	10%
IVB	10%	0%

rate in patients who underwent surgery after induction therapies (15% vs. 9.9%); however, this study showed the feasibility and safety of robotic approach even after neoadjuvant chemo-radiotherapy^[14].

The 30-day mortality rate of the entire population examined in this review is 0.25% (range 0%-4.9%). According to a recent meta-analysis conducted by O'Sullivan *et al.*^[19], the mortality rate is lower for patients who underwent robotic surgery compared to VATS or Open approaches with an overall protective effect of robotic over thoracotomy [OR: 0.53, 95%CI: 0.33-0.85 ($P = 0.008$)] and over VATS [OR: 0.61, 95%CI: 0.45-0.83 ($P < 0.001$)]. Notwithstanding these results should be thoughtfully considered, given that a possible selection bias in robotic cohort may have occurred, data on short-term outcomes of robotic surgery are very interesting.

Analysing the long-term results, the overall and stage-specific survival of robotic lobectomy are consistent with data reported by Goldstraw *et al.*^[20], which were mainly obtained by open surgery [Table 3].

According to the largest multicentre series of robotic lobectomy analyses by Cerfolio *et al.*^[15], which also included many other examined cohorts, the OS of patients who had completely resected NSCLC via robotic lobectomy is favourable compared to open surgery. One possible explanation proposed by the authors is a reduction of immunocompromised state after MIS surgery.

Moreover, the authors stated that DFS of robotic cohort is promising, especially in case of N2 disease. This is probably due to the easier and more precise dissection of lymph node during robotic surgery, which also leads to superior upstaging compared to VATS, improved staging and greater chance to undergo adjuvant chemotherapy^[21].

Our review reports good short- and long-term outcomes after robotic lobectomy for NSCLC, which combines the benefits of MIS with the accuracy of open surgery in stage-assessment, showing an overall and stage-specific OS comparable with that reported by IASLC database.

DECLARATIONS

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Authors' contributions

Conception and design, collection and assembly of data, data analysis and interpretation: Ricciardi S

Administrative support: Melfi FMA, Davini F

Provision of study materials or patients: Davini F, Romano G, Zirafa CC

Manuscript writing and final approval of manuscript: Ricciardi S, Davini F, Zirafa CC, Romano G, Melfi FMA

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Prof. Melfi is an official proctor for Intuitive Surgical. Drs. Davini, Ricciardi, Zirafa and Romano have no conflict of interest or financial ties to disclose.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Milestones in robotic colorectal surgery development: an historical overview

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Abstract

The present article is a historical review intended to trace the most important phases in the development of robotic surgical technology, with a special focus on colorectal surgery. The initial section considers the origin and some etymological aspects of the word "robot". Then, a historical overview traces the development of robotic technology in industry and its implementation within the operating theatres. Finally, the first publications concerning robot-assisted colon and rectal surgery are reported together with a brief state of the art about this issue.

Keywords: Robotic surgery, colorectal surgery, history

INTRODUCTION

In the contemporary world, the surprising and fascinating development of digital electronic technologies has determined so many changes in all aspects of human life that we now speak of a "digital revolution". An



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evident result of these impressive advances is certainly represented by the widespread use of robots. With this term, we refer to a large variety of machines with very different purposes and levels of complexity, from industrial manufacturing systems to humanoids provided with artificial intelligence. Over time, robotic technology has been naturally implemented also in the operating theatres, becoming one of the most debated topics in surgery over the last years. In the present article, we focus the observation field to general surgery, trying to trace the most important phases in the development of robotics in colorectal surgery.

DEFINITION AND ETYMOLOGY

The word “robot” is used to indicate a programmable machine able to carry out several tasks in aid of, or in place of, men with a variable degree of autonomy. It comes from the Czech noun “robota”, for forced labor or hard work, reminding of the status of serfdom in the feudal society, and sharing the same radical of the words meaning “work” in many current Slavic languages, such as Polish, Ukrainian, and Russian^[1].

The Czech writer Karel Čapek first used this term in his science fiction play titled “R.U.R.” (Rossum’s Universal Robots), published in 1920. This work deals with artificial workers, indistinguishable from men, produced from synthetic organic matter with the purpose of freeing mankind from physical fatigue. However, “robots” rapidly spread all over, start rebelling against men, and conquer the world.

Later, in 1943, the visionary American writer Isaac Asimov first used the word “robotics” in his science fiction story titled “Runaround”. Here, he established the three “Laws of Robotics”, a set of rules hardwired into the artificial brain of autonomous humanoid robots to underlie their behavior and prevent them from rebelling against their creators.

Hence, since their origin, two main concepts converge into the terms “robot” and “robotics”: work in support of men and the need of control by the latter.

HISTORY

Knowing the history of the implementation of robotic technology in surgery is useful for appreciating current advances in this field. Here, some important landmarks are reported to offer a general overview.

Ancient times: “automata”

From ancient times, the idea of self-operating machines, usually indicated as “automata”, is present in all cultures, from west to east.

The word “automaton” (plural “automata”) comes from the Greek word “αὐτόματον”, a neuter noun meaning “something self-acting”, which was first used by Homer in the Iliad referring to self-opening doors and self-moving wheeled tripods.

Several myths of the Greek and Roman tradition deal with “automata”. In the Iliad, Homer tells that Hephaestus, the god of fire, forges, metallurgy, and sculpture, constructed golden handmaids to help him in his forge on the Island of Lemnos. In the “Metamorphoses”, Ovid reports the myth of Pygmalion, a sculptor falling in love with his statue, Galatea, who was transformed into an animated creature by the goddess Aphrodite to fulfill Pygmalion’s prayer.

Halfway around the world, in ancient China, during the Zhou Dynasty (1023-957 BC), the artificer Yan Shi showed to King Mu a human-like machine that could move and sing^[2,3].

Several Greek mathematicians were known for constructing automata. The first automaton was built by Archytas of Tarentum (428-347 BC), and it consisted of a pigeon-shaped steam-operated flying machine.

Ctesibius of Alexandria (285-222 BC) was known to have built many human figures able to move and drink, as well as a black bird singing by means of a water flow. Moreover, Heron of Alexandria (10 BC-70 AD) conceived and constructed an entire theatre scene played by automata^[3,4].

In 949 AD, Liutprand of Cremona visited Constantinople and described the automata of Emperor Theophilos' palace, including metal lions striking the ground with their tails and roaring with open mouth and quivering tongue^[5].

In the Islamic world, the polymath Al-Jazari (1136-1206 AD) wrote a treatise where he described several automata he had designed and constructed, including automated musicians conceived to amuse royal guests^[3].

During the Renaissance, several inventors were dedicated to the construction of automata, such as Giovanni Fontana (1395-1454 AD), who designed automatic war machines capable of throwing bombs, and Leonardo da Vinci (1452-1519 AD), who designed a mechanic knight able to stand up and sit down, wave its arms, and move his head and jaws^[4].

However, the real progress in the construction of modern robots was reached with the Industrial Revolution and the development of calculators, and it was surprising.

From industry to surgery

At the origin of the development of robotic technology during the 20th century, there was the concept of "telepresence", intended as the idea that people can appear, receive stimulations, and produce some effects in a place other than their real location as if they were really present. This idea animated the development of the first robotic arms intended to be used in hostile environments, such as the ocean floor, or to manipulate hazardous materials^[3].

Already in 1951, engineer Raymond Goertz designed the first teleoperated articulated arm for the United States Atomic Energy Commission to handle radioactive material safely and reduce the risks for personnel. This system was a manipulator using just pulleys and cables as mechanical coupling between operator and machine, but it already represented a major progress in terms of design and feedback technology^[6,7].

In 1954, engineer George Devol patented a programmable robotic system designed for transferring objects and conceived for a large variety of purposes. From this initial project, he developed the world's first industrial robot, Unimate. He also co-founded with engineer Joseph Engelberger the world's first robotics company, Unimation, located in Danbury, Connecticut, to produce Unimate^[7,8].

In 1961, the first Unimate robot was installed in a General Motors factory in New Jersey and consisted of a robotic arm for lifting hot metal objects from die-casting machines and stacking them. Several automobile companies soon understood the potential of this technology, and large-scale production of this robot started^[7,8].

In 1969, Victor Scheinman, a researcher of the Stanford Artificial Intelligence Laboratory, developed the "Stanford Arm". It was an all-electric, computer-controlled, six-axis articulated robotic arm, able to follow random trajectories and perform a series of instructions, unlike previous machines, which moved along one fixed trajectory and performed only one task repeatedly. Indeed, the "Stanford Arm" was specifically designed to widen the application of robots to complex tasks, such as assembly and arc welding. Its potential applications were proved in 1974, when a sensor guided experimental version of this robotic arm managed to assemble a car water pump without any human intervention^[7-9].

In 1977, Scheinman sold his invention to Unimation. On this basis, Unimation collaborated with General Motors and developed the Programmable Universal Manipulation Arm (PUMA), which represented the basis for the production of a series of successful industrial robots^[7-9].

With the production of PUMA, the robotic technology entered the operating theatre. Indeed, the first use of a robot in a surgical procedure was documented in 1985 by Kwoh *et al.*^[10], who reported a CT-guided stereotactic biopsy of a brain tumor performed in a 52-year-old male patient using a Unimate PUMA 200 robotic arm at the Memorial Medical Center, Long Beach, California.

Surgical robots spreading

Since the second half of the 1980s, several robotic surgical systems started to appear in the operating theatres. In 1988, researchers from the Imperial College of London developed the PROBOT system to perform prostatic resections. In 1992, Integrated Surgical Systems, in collaboration with IBM, released the ROBODOC system, successfully used for milling the femur in hip replacement procedures^[1,3,11-14].

In the same period, a group of researchers of the National Aeronautics and Space Administration (NASA) working on virtual reality started collaborating with researchers of the Stanford Research Institute (SRI) working on accurate surgical telemanipulators for open microsurgery. After the presentation of Jacques Perrisat's laparoscopic cholecystectomy at the Society of American Gastrointestinal and Endoscopic Surgeons in 1989, the SRI developers were urged to adapt their telepresence surgical system to the new laparoscopic approach, which was immediately regarded as a perfect field of implementation for robotic technology^[14].

Meanwhile, the U.S. Defense Advanced Research Projects Agency (DARPA) started a research program to develop a robotic surgical telemanipulator mounted on a mobile armored vehicle and remotely operated by a surgeon at a rear facility area. The aim of this project was to allow surgeons to control life-threatening injuries on the battlefield and stabilize injured soldiers before they were taken away. For this purpose, DARPA funded SRI, which developed a robotic system proving successful in performing complex surgical procedures in animal models. Finally, the project was not completed for human use, but it provided a solid basis for the development of the robotic systems later used in surgery^[14].

In 1993, Computer Motion, funded by NASA and DARPA, released the Automated Endoscopic System for Optimal Positioning (AESOP), an intern replacement voice-controlled robotic arm allowing the automatic control of a camera during laparoscopic surgery^[14].

In 1996, the same company released ZEUS, a surgical system consisting of three robotic arms attached to the operating table, one of which was an AESOP, with originally six degrees of freedom (later seven) and a monitor provided console for remote control^[14]. In 2001, it was used by Pr. Marescaux *et al.*^[15] operating in New York to perform the first transatlantic robotic cholecystectomy in a 68-year-old female patient laying on the operating table in Strasbourg, the so-called "Lindbergh Operation"^[15,16].

In 1995, Drs. Fred Moll and John Freund, together with engineer Robert Young, founded Intuitive Surgical after negotiating for the intellectual properties of SRI robotic surgical systems. On this basis, Intuitive Surgical developed the first prototype of the da Vinci surgical system in 1997. After being ameliorated, the system received US Food and Drug Administration approval in 2000. After passing through several versions, it currently represents the most widespread and used master-slave robotic surgical system in general surgery^[14].

It must be noted that several other robotic systems have been used in surgery thus far, but here we only select the ones appearing to mark more deeply the evolution of robotic technology in operating rooms.

Main types of robots implemented in surgery

Some authors have distinguished the different robotic systems thus far used in surgery into three main types^[12]:

1. “Precise path systems” include robots previously programmed to perform predefined and repetitive tasks, such as several types of devices used for prostatic transurethral resections and to puncture the renal calyces.
2. “Intern replacement systems” include robotic devices intended to replace surgical assistants in tasks requiring dexterity and stability, such as the AESOP system.
3. “Master-slave systems” have several robotic arms remotely controlled by a surgeon through a computer console, mimicking precisely on the patient laying on the operating table the movements carried out by the surgeon at the console, and never moving without the surgeon’s guidance. In this context, the da Vinci surgical system has become paradigmatic.

Clearly, this is not a complete summary, but it is useful to set out some important phases in the implementation of robotic technology in surgery.

MILESTONES IN ROBOTIC COLORECTAL SURGERY

The first publications available in the literature concerning robotic colorectal surgery are reported here. A brief state of the art about the robotic surgery of colon and rectum is also provided.

Robotic surgery of the colon

The first cases of robot-assisted colectomies were published in 2002^[17]. In particular, Weber *et al.*^[18] reported one case of sigmoid colectomy for diverticular disease in a 50-year-old female patient, and one case of right hemicolectomy for cecal diverticulitis in a 43-year-old male patient. In both procedures, a da Vinci surgical system was used for large bowel mobilization, whereas colonic section and vascular ligations were accomplished with a laparoscopic-assisted technique, and anastomoses were performed extracorporeally. Moreover, the same surgical team published in the same year a comparative study reporting 15 laparoscopic colectomies performed using an AESOP 3000 robotic camera holder and 11 not robot-assisted laparoscopic colectomies^[19].

The first cases of patients with colon cancer undergoing robot-assisted surgery with a master-slave robotic system were reported by Hashizume *et al.*^[20] in 2002, and they consisted in one ileocecal resection, one left hemicolectomy, and one sigmoidectomy performed by means of da Vinci technology for cecal, descending colon, and sigmoid colon cancer, respectively^[17].

Since then, many studies concerning robot-assisted surgery of the colon have been published, marking a progressive amelioration of technical practices and a wide spread of competences. Among these studies, a certain attention should be paid to a case series of right and left colectomies published by Rawlings *et al.*^[21] in 2007, where the authors reported the first cases of robot-assisted side-to-side intracorporeal anastomosis after right colectomy.

The advantages provided by robotic systems, such as stable, immersive, and three-dimensional view; better dexterity due to seven degrees of freedom; and ambidextrous capabilities, seem to offer the potential to overcome the limitations of conventional laparoscopy, mostly due to less favorable ergonomic features. Therefore, over time, many studies were carried out to compare the outcomes of robotic and laparoscopic surgery of the colon, but their results are contrasting and clear conclusions are not possible.

In particular, a recent systematic review with meta-analysis published by Ng *et al.*^[22] in 2009 tried to state whether robot-assisted laparoscopic surgery had better outcomes compared to conventional laparoscopy in colorectal cancer treatment. The authors included six randomized clinical trials (RCTs) and 67 prospective/retrospective cohort studies and case-controlled studies, demonstrating that robotic surgery was superior to

conventional laparoscopy in terms of all-cause mortality, incidence of surgical site infection, intraoperative blood loss, length of hospital stay, and time to oral diet, but inferior in terms of operative time. No significant difference was found in terms of anastomotic leak and disease recurrence. However, regarding the RCTs subgroup of the same study, no significant difference was found except for operative time, which confirms the current absence of evident advantages in favor of one approach or the other in colon cancer surgery.

Robotic surgery of the rectum

In 2001, Cadière *et al.*^[23] first described the use of robotic technology in rectal surgery, reporting three transanal rectal resections performed by introducing through the anus two robotic arms for manipulations and a standard laparoscope held by an assistant for viewing. In 2003, Delaney *et al.*^[24] reported the first case of transabdominal robot-assisted rectopexy for rectal prolapse, while Giulianotti *et al.*^[25] reported the first cases (six) of robot-assisted rectal anterior resection for rectal cancer^[17]. Notably, both types of operations mentioned above were performed with Intuitive Surgical systems. In the same year, Hildebrandt *et al.*^[26] also reported the implementation of an AESOP 3000 robotic arm in the surgical treatment of rectal cancer to perform two laparoscopic rectal anterior resections.

The advantages provided by the robotic systems in terms of view and manipulations seemed even more evident in the case of rectal surgery because of the narrow, deep, and fixed operating field represented by the pelvis. Therefore, a growing number of robot-assisted procedures in rectal surgery, especially for cancer, has been reported, with many authors trying to compare the outcomes of robotic surgery and conventional laparoscopy.

Focusing on oncological surgery and setting aside the numerous retrospective studies available, seven RCTs^[27-33] comparing robotic and laparoscopic surgery of the rectum were carried out to present, and their results were summarized by Liao *et al.*^[34] in a systematic review with meta-analysis published in 2019. Notably, these authors did not find any significant difference in terms of circumferential resection margins and quality of mesorectal excision, as well as in terms of proximal resection margins and number of retrieved lymph nodes, even if a significant heterogeneity of data was found for these two latter issues. On the contrary, distal resection margins were significantly longer in patients undergoing robotic surgery, although the heterogeneity of data was still considered high.

Particular attention must be paid to the Robotic vs. Laparoscopic Resection for Rectal Cancer (ROLARR) study^[31], the largest and highest quality trial currently available. In particular, it concluded there was no significant difference between robotic and conventional laparoscopic surgery in terms of conversion rate, circumferential resection margins, mesorectal resection quality, and postoperative complications within 30 days and 6 months after operation. In addition, the authors performed a costs analysis showing significantly higher costs for robotic surgery, but the absolute difference was just slightly in favor of conventional laparoscopy among the patients with complete data.

Moreover, among the trials cited above, only Patrìti *et al.*^[28] reported overall survival and disease-free survival, showing no significant differences, but stressing a trend towards better disease-free survival in robotic surgery and concluding in favor of the latter in the case of total mesorectal excision but not in case of partial mesorectal excision.

Limitations of robotic technology to present

Even if robotic technology provides several objective advantages in terms of working conditions and offers a faster adaptation compared to conventional laparoscopy, it also presents some limitations, the most relevant

of which are represented by time of robotic setting, lack of both tactile sensation and tension feedback, and high costs^[35].

Robot docking and collisions among instruments partially explain the longer operating time frequently reported for robotic surgery, but an experienced team may overcome this limitation, as can the implementation of the latest technological innovations. The latter might also allow overcoming the absence of tactile feedback of robotic systems, currently partially arranged by means of the ameliorated view they provide^[35].

For what concerns high costs, it can be remarked that the implementation of conventional laparoscopy was also very expensive at the beginning, but it provided a number of advantages in terms of postoperative outcomes, which justified its spread. Clearly, the implementation of robotic surgery is more expensive, but the evaluation of eventual clear benefits for patients and surgeons could motivate its use as well^[35].

CONCLUSION

The implementation of robotic technology in general surgery represented the inevitable outlet of an astonishing technological development. It has proved to be feasible and safe, with several operating advantages for surgeons. However, clear advantages in terms of patient outcomes have not yet been demonstrated after the implementation of robotic systems in colorectal surgery.

To evaluate the overall impact of robotic technology in colorectal surgery, further studies with high levels of evidence are necessary, as well as those implementing the new robotic technologies already appearing in operating theatres.

DECLARATIONS

Authors' contributions

Conception: Genova P, Pantuso G, de'Angelis N

Literature review: Genova P, Pantuso G, Abdalla S, Memeo R, Gaiani F, Gavriilidis P, de'Angelis N

Writing: Genova P (Genova P and Gavriilidis P for the chapter "Ancient times: automata")

Revision: Genova P, Pantuso G, Abdalla S, Memeo R, Gaiani F, Gavriilidis P, de'Angelis N

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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Editor's note:

This article has been retracted.

Original Article

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Diagnostic value of erythrocyte sedimentation rate levels as a predictor of staple-line leakage in bariatric surgery

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Abstract

Aim: Bariatric surgery is an effective treatment for morbid obesity that has inevitable complications including postoperative bleeding and staple-line leakage. Erythrocyte sedimentation rate (ESR) can be a clinical indicator for prediction of leakage.

Methods: This retrospective cohort study was done on 1999 patients who underwent sleeve gastrectomy in Erfan Niyayesh Hospital, Tehran, Iran. ESR levels of patients were evaluated in cases which had postoperative leak. Statistical analyses were performed using SPSS software.

Results: Among the 2350 patients, 50 subjects experienced gastric leak (2.12%). ESR mean was 73.1 mm/h for cases, statistically significantly higher in patients with leakage compared to the control group. In addition, ESR serum level mean was 31.34 mm/h for control groups. Other variables including C-reactive protein and platelet count were not statistically significant.

Conclusion: Higher ESR serum level can be seen in various conditions, and, in obese patients who undergo bariatric surgery, it can be a reliable predictor for postoperative gastric leak complication.

Keywords: Erythrocyte sedimentation rate, postoperative leak, sleeve gastrectomy



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INTRODUCTION

Bariatric surgery has become one of the most effective treatments for morbid obesity, with extremely good long-term results on weight loss, co-morbidities, and low mortality as well as postoperative complications rate^[1]. Bariatric surgery for morbid obesity has improved in the last fifteen years^[2]. According to every published report, bariatric surgery is one of the safest operations with a complication rate of less than 1%^[3,4]. However, knowledge about its anatomic reconstruction, the physiologic effects of bariatric surgery, and the prevention and management of complications after a bariatric procedure have not been directly incorporated into general procedure preparation programs^[5,6]. Hence, general surgeons should expand their basic anatomic, clinical, and surgical understanding because they might face postoperatively acute or chronic complications in their patients^[6]. Bariatric surgery can cause early complications including primarily staple-line leakage and bleeding in the immediate postoperative days. Late postoperative complications include abscess development or delayed postoperative staple-line leakage with fistula as well as sleeve stenosis. In addition, some patients can develop a rare case of sleeve gastrectomy, which is deep vein thrombosis^[7].

As mentioned, gastrointestinal staple-line leakage remains one of the most unavoidable complications after the procedure, resulting in increased healthcare cost and postoperative pain in patients^[8]. According to several meta-analyses, gastrointestinal leak rate has been estimated to range from 2.5% to 7% after various types of bariatric surgery^[6-9]. Postoperative gastrointestinal leak has been constantly dropping recently and its occurrence is low^[10]; nonetheless, leakage is still a principal complication, leading to increase morbidity and mortality rate. Various surgeons have employed different interventions for detecting leaks either intraoperatively or postoperatively such as placement of an orogastric tube with distention of the gastric pouch with air, endoscopy with carbon dioxide insufflations, and methylene blue dye^[6].

Researchers have recently found that, in patients with low BMI, postoperative increased heart rate (tachycardia > 120 bpm), evidence of respiratory distress, and decreased hemoglobin were significantly associated with bleeding^[11,12]. Alizadeh *et al.*^[13] reported that oxygen dependency, hypoalbumenia, sleep apnea, hypertension, and diabetes were critical factors related to increased risk of leak^[13]. In addition, preoperative platelet count, INR, and systolic blood pressure were not significantly related to postoperative bleeding^[12]. On the other side, the association between preoperative partial thromboplastin time and bleeding was significant^[12]. Burgos *et al.*^[11] stated that increased white blood cell (WBC) and C-reactive protein (CRP) levels, abdominal pain, tachycardia, tachypnea, and fever are more common in subjects with gastric leak^[11].

From the clinical perspective, an erythrocyte sedimentation rate (ESR) is one of the blood tests that is usually ordered by physicians for patients with symptoms such as inflammation in the body, headaches, fever, joint stiffness, neck or shoulder pain, weight loss, loss of appetite, anemia, and fever^[14,15].

Higher ESR levels may be associated with a medical condition, such as infection or inflammation (especially inflammatory bowel disease), rheumatoid arthritis, cardiovascular or kidney disease, and some types of cancers. Higher ESR levels do not necessarily mean that the patients have a medical condition that requires treatment^[15]. For example, certain medications and dietary supplements can also affect ESR results, including oral contraceptives, cortisone, vitamin A, and aspirin. A moderate ESR may indicate pregnancy, menstruation, or anemia, rather than an inflammatory disease. A slow ESR may indicate a blood disorder such as polycythemia, sickle cell anemia, and leukocytosis^[14,15].

The main purpose of this study was to evaluate correlations of ESR, CRP, and platelet count with incidence of intermediate gastrointestinal leak in obese subjects who underwent sleeve gastrectomy.

METHODS

Data source

We performed a retrospective cohort study using the database of Erfan Niayesh Hospital bariatric procedures performed by Taha Anbara, Laparoscopic Surgeon, MD.

Surgical procedure

Sleeve gastrectomy was performed on all subjects according to the standard protocol and in a similar method by a specific surgeon with similar tools during the same duration. After prep and draping under GA, a 10-mm trocar canula (Covidien, Cincinnati, OH) is inserted above the umbilicus. Then, three 5-mm trocar canulas and one 15-mm canula (Covidien, Cincinnati, OH) are inserted under direct vision in the proper place. The gastrocholic ligament is divided with ligature. Then, the sleeve gastrectomy is done with seven 4.5-mm staples (black cartridges). The divided part of the stomach is taken out later and the place of staple line is sutured with 2-0 yarn. Afterwards, the drain is placed at gastrectomy site. The canulas are taken out later under direct sight and then, when homeostasis is reliable, abdominal gas is drained and the place of Canula 10 is repaired. To determine leakage, we transiently block the flow into the duodenum with long intestinal forceps at the pyloric channel. The removed specimen, which is removed easily through the 15-mm port at the right upper abdominal quadrant, is sent for histological analysis. Finally, one silastic drain is always left at side of the gastric suture line.

Clinical evaluation

Clinical sign and symptoms were repeatedly surveyed for all subjects every 6 h after surgery. Intraoperative gastrointestinal leakage was not observed during procedure in any subjects.

Study design and population

Clinical data on 199 adult obese subjects who underwent sleeve gastrectomy were evaluated according to the Current Procedural Terminology code: LSG (43,775). Approval for the use of the data in this study was obtained from the Erfan-Niyayesh Hospital. Subjects were categorized into two groups, those who experienced postoperative gastrointestinal leakage (Cases) and those without any types of leakage, whether intraoperative or after procedure (Control). Preoperative co-morbidities and characteristics were examined to determine predictive factors of leakage. Oral contrast was given during the study and the contrast was followed when it went from the mouth to the small intestine. Emergent, revisional, and converted cases were excluded. The time and location of appearance and closure of leakages were diligently recorded in all cases.

Definition of leakage

The UK Surgical Infection Study Group has defined a standard definition of anastomotic leakage: “the leak of luminal contents from a surgical join between two hollow viscera”. It may also demonstrate a gastrointestinal leak in a suture line around the organ. According to the time of leakage appearance, they have previously been classified^[14] as follows: early (leaks appearing 1-3 days after procedure), intermediate (leaks appearing four days to a week after surgery), and late (leaks appearing more than one week after procedure).

Patients

Fifty cases who had postoperative gastrointestinal leakage were considered in the study as well as 149 control cases (ratio 3:1) randomly selected to increase the reliability of the study. The information of control cases was extracted from the medical records of Erfan-Niyayesh Hospital. All cases underwent sleeve gastrectomy during 2017-2019 in Erfan-Niyayesh Hospital under supervision of the same surgeon with the same tools. The variables used in the multivariate analyses included demographic data (BMI, age, and gender), preoperative co-morbidities, procedural type, and various intraoperative and postoperative interventions.

Table 1. The distribution of study variables

Variables	Total (n = 199)	Case (n = 50)	Control (n = 149)
Sex (count/percent)			
Male	60 (30.2%)	15 (30%)	45 (30.2%)
Female	139 (69.8%)	35 (70%)	104 (69.8%)
Age (mean)	38.15	37.32	38.42
ESR (mean)	41.83	73.1	31.34

ESR: Erythrocyte sedimentation rate

Statistical analysis

Adjusted and unadjusted binary logistic regression models were used to evaluate effects of independent variables on leaking outcome (0 = no, 1 = yes). Independent variables included sex, age, and ESR. The significance level was defined as 0.05 ($\alpha = 0.05$). Both adjusted and unadjusted variables with significant levels were included in the final models and are reported below. Statistical analysis was performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL).

The final predicting model for leaking outcome was designed using the following regression model:

$$\log[P_x / (1 - P_x)] = a + b_i X_i$$

The final adjusted prediction model of log (odds) for leaking outcome was calculated using the following equation:

$$y = (-3.576) + 0.50 (ESR)$$

RESULTS

We investigated, among the 2,350 patients who underwent sleeve gastrectomy from 2016 to 2019, 50 subjects who experienced gastric leak (2.12%). The total sample size was 199 patients, including 50 cases experiencing leak and 149 controls (randomized from 2,350 patients). Overall, 69.8% of the cohort, 70% of cases and 69.8% of controls, were females. The mean age for the cohort was 38.15 (minimum 12 years old and maximum 63 years old). The mean ESR was 73.1 mm/h for cases, which is statistically significantly higher in patients with leakage compared to the control group. In addition, ESR serum level mean was 31.34 mm/h for control groups. More descriptive results are reported in [Table 1](#).

The results of adjusted and unadjusted logistic regression are reported in [Table 2](#). Females were taken as reference group due to bigger proportion in the sample. The only independent variable which had significant association with staple-line leakage was ESR (OR = 1.051). This means that, for every 1 unit increase of ESR, the odds for staple-line leakage occurrence increases by 5.1%.

DISCUSSION

The sleeve gastrectomy procedure has been popularly employed for the management of morbid obesity and this operation has a series of inevitable complications. Staple-line leakage is one of these complications, with an incidence ranging from 7% to 25% after bariatric surgery^[6]. Although researchers have mentioned various approaches, surgeons utilize the endoscopic approaches, such as stent inserting, clips, and biologic glue^[16]. This study comprised our experiences with 199 patients, with or without staple-line leakage, after sleeve gastrectomy. The final adjusted prediction model of log (odds) for leaking outcome can be used to predict leaking outcome. Exponential of (y) gives odds of occurrence of leaking for each patient with archived ESR. It should be noted that, because of the impact of other factors affecting on staple-line leakage outcome, this model might not be 100% precise.

Table 2. Binary logistic regression models results (odds ratio)

Variables	Unadjusted model		Adjusted model	
	OR (95%CI)	P value	OR (95%CI)	P value
Sex	0.99 (0.49-1.99)	0.979	0.94 (0.38-2.34)	0.909
Age	0.98 (0.95-1.02)	0.490	0.95 (0.917-1.01)	0.056
ESR	1.051 (1.036-1.066)	0.000	1.054 (1.038-1.070)	0.000

ESR: Erythrocyte sedimentation rate; OR: odds ratio

According to the results, ESR serum level in patients with leak after sleeve gastrectomy was significantly increased in comparison with ESR levels of patients without any complications after the surgery. The mean ESR serum levels were 73.1 mm/h for cases and 31.34 mm/h for controls.

As mentioned above, high ESR serum levels can be seen in various conditions such as cardiovascular and kidney disease and obstructive sleep apnea^[14,15]. However, after bariatric surgery, patients with obesity start to lose weight, which may lead to an increase in ESR serum levels, but mean ESR in patients with leak compared to control group was significantly higher. Thus, for every 1 unit increase in ESR serum levels, the odds for leakage occurrence increase by 5.1% in patients after bariatric surgery. The normal range of ESR for men is 0-22 mm/h and 0-29 mm/h for women^[15], but in subjects with obesity, due to a series of interactions, it can be elevated. Macrophages and adipose tissue secrete cytokines and interleukins, resulting in stimulation of liver to produce fibrinogen, CRP, and haptoglobin, which in turn elevate ESR serum levels during inflammation [Figure 1]^[15]. Therefore, with this diagnostic value of ESR, surgeons can employ ESR serum levels immediately after procedure, instead of common interventions that might increase the cost and duration of treatment^[6]. In vulnerable patients with abnormal ESR levels, a series of technical recommendations can be done to prevent leakage after operation, including use a 40 Fr size or more bougie, initiate the gastric transection 5-6 cm from the pylorus, use proper cartridge colors from antrum to fundus, reinforce the staple line with buttress material^[5], order an appropriate staple line^[6], perform an intraoperative methylene blue test, remove the crotch staples, maintain suitable traction on the stomach before firing, avert from the angle of His (at least 1 cm), and check the staple line bleeding during the procedure.

Although gastric leakage can be caused by either mechanical or ischemic reasons, ESR serum levels might be a reliable predictor for postoperative leakage. Hence, in patients with higher ESR, more sedulous management (leaving a shorter antrum and using a smaller bougie) can be performed by surgeons and this may open a new chapter in terms of personalized surgery with fewer cases of leak complications among subjects. Previous studies have not paid sufficient attention to the molecular dimension of gastric leak; instead, most studies have focused on mechanical dimension and the management of this complication. Researchers have found that a greater bougie is related to a leakage rate of 0.6% in comparison with those who used smaller sizes whose leak rate was 2.8%^[16]. However, Keren *et al.*^[17] reported normal ESR levels of patients with gastric leakage, which is in contrast to our findings.

Other variables including sex, age, platelet count, and CRP serum level were not significantly different compared to control patients. In line with these results, Keren *et al.*^[17] in 2015 and Surace *et al.*^[18] in 2011 reported that gastric leak after sleeve gastrectomy presents no correlation with serum levels of CRP and WBC^[17,18]. Nevertheless, more studies are warranted to address the question of why ESR serum level has been increased without any significant changes in CRP levels.

In conclusions, this study reports the clinical correlation of gastric leakage and platelet count, ESR, and CRP serum levels and gives practical instructions to prevent and manage leaks after sleeve gastrectomy. In short, these recommendations are: (1) use greater size of bougie; (2) begin the gastric transection 5-6 cm from

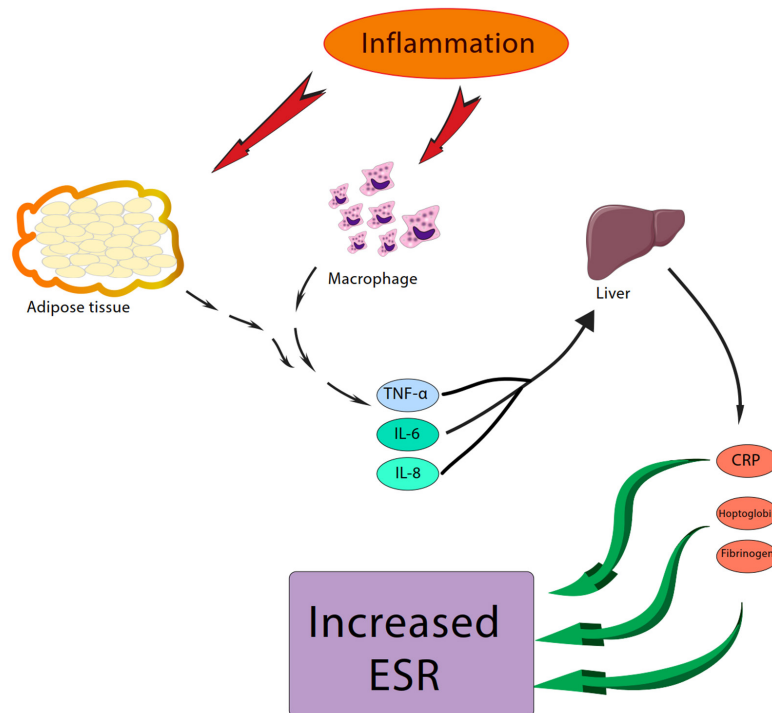


Figure 1. The impacts of inflammation on serum level of erythrocyte sedimentation rate (ESR)

the pylorus; (3) use suitable cartridge colors; (4) reinforce the staple line with buttress material; (5) follow an appropriate staple line; (6) remove the crotch staples; (7) maintain adequate traction on the stomach before firing; (8) keep distance from the angle of His; (9) check the staple line bleeding; and (10) perform a methylene blue test during the procedure.

DECLARATIONS

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Authors' contributions

Designed and performed experiments: Kheirvari M, Eshghjoo S

Gathered the data and performed the numerical simulations: Yazdannasab M, Hosseini S

Analysed data and performed bioinformatic analyses: Akbarzadeh I

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Editorial

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Metabolic and bariatric surgery: diabetes - a decade of discovery

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INTRODUCTION

Diabetes is a progressive and chronic condition that affects a growing percentage of the population each year. Obesity is considered to be the central risk factor in the development of type 2 diabetes mellitus (T2DM) in adults. In 2019, the top three countries for diabetes prevalence were found to be China, India, and the United States, affecting 116, 77, and 31 million adults, respectively^[1,2]. More than 420 million adults are affected worldwide, representing a significant burden to healthcare systems as well as the wellbeing of the global population^[3].

Metabolic and Bariatric surgery for the treatment of T2DM has been of significant interest in recent years. At the start of the decade (2011), the International Diabetes Federation wrote a consensus statement promoting the use of bariatric surgery in obese patients with poorly controlled diabetes^[4]. However, as the number of adults with T2DM worldwide grows exponentially each year, metabolic and bariatric surgery for treatment remains a topic of substantial interest. In 2019, the American Society for Metabolic and Bariatric Surgery (ASMBS) held its annual Obesity Week Conference, electing diabetes as the central topic. The presidential address (Eric J. DeMaria, MD Fellow of the American Society of Metabolic and Bariatric Surgery) at this meeting highlighted a growing effort to raise awareness on the beneficial effects of surgery for glycemic control. Dr. DeMaria suggested increasingly referring to metabolic surgery with patients as “diabetes surgery” in order to promote the concept in the general population. As we continue to raise awareness of the benefits of metabolic and bariatric surgery to those in the healthcare field as well as the general population, it is important to evaluate what we have learned and what has yet to be discovered.



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A DECADE OF DISCOVERY

Historically, the primary treatment for diabetes was through behavioral modification and pharmacologic treatment. Frequently, combination therapy would be necessary, increasing the number of medications prescribed to patients^[5]. Although glucose control was improved, management often became more challenging for clinicians, and many patients were burdened with increased costs, intolerable side effects, and poor compliance. The overall goal was always to improve glycemic control; however, remission or cure of the disease was often thought to be unattainable. Even with maximal drug therapy, some patients still struggled with achieving desired HbA1C levels. Given these difficulties in management, the beneficial effects of surgery on glycemic control garnered immediate attention.

While observational studies were abundant, the emergence of several randomized controlled trials (with long-term follow up) helped to raise awareness in both the medical and surgical communities regarding the significant diabetic improvement seen after metabolic and bariatric surgery. Not only was surgery found to be effective, but it showed superiority to medical therapy in glycemic control, medication reduction, and weight loss^[6,7]. In 134 patients at five-year follow up, the randomized STAMPEDE trial (Surgical Treatment and Medications Potentially Eradicate Diabetes Effectively) demonstrated sustained remission of diabetes (HbA1C < 6.0% without glucose lowering medications) in 22% of the gastric bypass group, 15% of the sleeve gastrectomy group, and 0% of the medical therapy group. Similarly, comparing medical treatment to surgery, Mingrone *et al.*^[7] found in 53 patients at five years that 42% of gastric bypass and 68% of biliopancreatic diversion patients were able to achieve remission of their diabetes (HbA1C < 6.5% without glucose lowering medications) while none of those in the medical treatment group had.

The outcomes from these as well as many other studies helped to broaden the awareness of surgery as a tool for the treatment of diabetes and extend this knowledge outside the surgical community. Given the overwhelming evidence, at the 2nd Diabetes Surgery Summit, a consensus was reached among international diabetes organizations to promote the use of bariatric surgery for type 2 diabetes^[8,9]. The endorsement was approved by many medical and surgical societies including the American Diabetes Association, the International Diabetes Federation, ASMBS, Diabetes UK, and The American College of Surgeons^[9]. The consensus stated that “metabolic surgery should be recommended to treat T2DM in patients with class III obesity [body mass index (BMI) ≥ 40 kg/m²] and in those with class II obesity (BMI 35.0-39.9 kg/m²) when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy. Surgery should also be considered for patients with T2DM and BMI 30.0-34.9 kg/m² if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications”^[8,9]. Despite many publications, it is a continued effort for surgeons to spread this knowledge to other physicians (primary care, endocrinology) as well as to insurance companies. The goal is to reach and obtain coverage for a greater number of patients who would benefit from bariatric and metabolic surgery.

RISK FACTORS FOR REMISSION

As we discovered the potential for the surgical improvement of diabetes, risk factors for failure of remission (or likelihood of relapse) also became evident. Increased age, longer duration of diabetes (> 8 years), preoperative insulin usage, number of oral antidiabetic medications at time of surgery, and poor preop glycemic control were found to adversely affect outcomes^[6,10-12]. It is theorized that these risk factors represent the pathologic concept of diminished β -cell reserve in the pancreas, and its ability to improve in response to metabolic surgery. These observations underscore the importance of intervening early with surgery in the progressive course of diabetes^[6,10].

Initial investigation into remission rates after sleeve gastrectomy by Schauer *et al.*^[6] found 14.9% of patients remained in remission at 5 years. However, much of the cohort in the Cleveland study was known to

have comparatively advanced diabetes, with mean preoperative HbA1C at 9.2 ± 1.5 , duration of disease of 8.5 ± 5.2 years, and 44% on insulin therapy preoperatively. In a study from Argentina, Viscido *et al.*^[13] found much higher rates of remission at five years post sleeve gastrectomy (71%) in their cohort of patients, of whom only 13% were on insulin preoperatively, and mean HbA1C was 7.15. As we might expect, of their patients who were taking insulin preoperatively, the remission rate at five years was much lower at 37.5%. Sánchez-Pernaute *et al.*^[14] further supported this finding in a study of 97 patients undergoing single anastomosis duodenal ileal bypass (SADI-S). Duodenal switch and SADI are regarded by many as the most efficacious surgeries for diabetes. However, in their study, we still observe a large disparity in remission rates in patients taking preoperative oral antidiabetics vs. insulin. Absolute remission rate in these two groups was 92.5% vs. 47% at one year, and 75% vs. 38.4% at five years^[14].

Indeed, we see large variability in the remission rates between studies, as a strong determining factor is the patient selection and the severity of preoperative diabetes. This is acknowledged by the authors of multiple studies when comparing their higher remission rates to that of the STAMPEDE trial, typically quoting lower HbA1C, shorter duration of disease, and lower use of insulin in their patient populations^[13]. The discerning reader must also be aware of the differing values that denote “remission” amongst the various studies, which can yield results that appear inflated when cutoffs are less stringent. Further multi-institutional studies inclusive of a broader, more generalizable range of patients with subgroup analysis will help to elucidate accurate remission rates.

CHOICE OF PROCEDURE

Sleeve gastrectomy is currently the most common procedure performed for weight loss. When evaluating the effectiveness of metabolic procedures on long-term diabetic improvement, current studies suggest anastomotic procedures to be more efficacious over restrictive procedures, with duodenal switch outperforming gastric bypass^[6,7]. However, many of the randomized controlled trials from which we abstract these data were not powered to detect significant differences between procedures. Considering this, Aminian *et al.*^[10] evaluated the pooled data from four randomized controlled trials^[6,15-17] of T2DM remission for sleeve and bypass (each providing at least five-year follow up data). Interestingly, they found that there was no significant difference between procedures, or, at most, if we assume a difference exists that the pooled power was insufficient to show, a 15% advantage in remission rate of bypass over sleeve would exist^[10].

In a larger, single center, triple blind, randomized controlled study from Norway, Hofsø *et al.*^[18] sought to compare the effects of bypass vs. sleeve on remission of T2DM in obese individuals while also looking at the improvement in β -cell function. With 107 patients at one-year follow up, they found a 75% remission rate for gastric bypass and 48% remission rate for sleeve gastrectomy. Interestingly, despite a higher rate of resolution with the bypass, the authors did not find a significant difference between procedures when they assessed improvement in β -cell function. This was tested by the validated method of intravenous glucose tolerance test.

Despite these results from randomized trials which tend to favor duodenal switch or gastric bypass, the most efficacious procedure does not always equate to be the best choice for all patients. It can be easy to lose sight of other mitigating variables when intending to follow the published evidence. At our practice, we agree it is essential to consider a variety of factors when discussing procedure choice with our patients. Clearly, there are several technical, nutritional, pathologic, pharmacologic, and behavioral factors that may dictate the appropriateness of one procedure over another. However, in terms of guiding the choice as it relates to metabolic improvement, it is important to consider the severity of the disease and ability of the pancreas' β -cell reserve to respond to the gastrointestinal modulatory effects of surgery.

While duodenal switch and bypass may trend toward the most optimal outcomes^[7,14], for a patient with advanced diabetes of long duration, the β -cell reserve of the pancreas is likely minimal and incapable of improving significantly regardless of the chosen operation. To further evaluate this, Aminian *et al.*^[19] examined a large cohort ($n = 900$) of patients in order to create the individualized metabolic surgery score. This score, which uses previously discussed preoperative risk factors for resolution of diabetes (duration, HbA1C, number of oral medications, and insulin use), categorizes T2DM into three stages of severity. What this score highlights is that in patients with severe T2DM (Diabetes > 10 years, multiple oral antidiabetic drugs + insulin, and HbA1C of 8%), both sleeve and bypass have similarly poor efficacy in diabetes improvement (12% long-term remission for both)^[10,19]. Thus, there is little evidence that choosing bypass over sleeve in this group of patients will lead to improved glycemic outcomes, and the most clinically safe procedure is likely the best choice. Similarly, yet at the other end of the spectrum, for patients with diabetes of minor severity, the cohort was observed to have high rates of diabetes remission at long-term follow up with both sleeve (74%) and bypass (92%)^[19]. Thus, while bypass had slightly higher rates of remission, the patient should be counseled that sleeve is also a very efficacious option. It is in the intermediate patients with moderate severity diabetes where bypass was observed to have significantly improved outcomes compared to sleeve. This difference is much more likely to be of clinical importance when choosing procedure. In the intermediate group, 60% of patients who underwent gastric bypass showed long-term diabetes remission compared to 35% of those who had sleeve gastrectomy^[19].

Recognizing the above when planning with the patient will help to set appropriate expectations for disease response in the postoperative period. Additionally, given that many patients with severe diabetes may also be poor operative candidates, it is important to remember that their metabolic response from sleeve gastrectomy is likely to be the same as with an anastomotic procedure, potentially allowing for a quicker and thus safer surgery. To avoid choosing a more advanced procedure for a patient who may not benefit from improved outcomes, it is important to consider the degree of their β -cell reserve and thus potential for improvement.

REVISIONAL SURGERY

Although many studies focus their investigation on the sustained remission of diabetes, we should not consider relapse a failure of treatment. Many patients with relapse still experience the benefit of improved glycemic control/A1C while requiring fewer medications^[20]. However, similar to obesity, diabetes is a chronic illness that requires a long-term strategy for treatment. Mingrone *et al.*^[7] found that, at five years, hyperglycemia relapsed in 44% of the 34 surgical patients who had achieved two-year remission (however, they maintained a mean HbA1c of 6.7). As follow up time increases, the proportion of patients who maintain diabetes remission decreases^[6,21] and further options for treatment must be considered. Just as we are increasingly recognizing revisional surgery as a necessary approach for patients who obtain inadequate results in the treatment of their obesity, a similar approach will likely hold true for diabetes.

The current data however do not support adequate analysis of a revisional approach. Studies have typically evaluated whether patients remain in remission at a defined follow up period. This has mainly allowed for comparison on the efficacy between procedures at five years or more. However, if we consider total number of remission years obtained, we may find that a combination of procedures yields greater lifetime remission than any primary procedure alone. We have a paucity of evidence regarding the role of revisional surgery in the treatment of T2DM^[20,22]. In a review of multiple studies on revisional bariatric surgery, Yan *et al.*^[23] demonstrated that, in the majority of cases, reoperation has a positive effect on both improvement in diabetes and further weight reduction. Unfortunately, these observational studies were of rather low power, without investigation of diabetes being the primary end point^[23]. We have yet to evaluate with high-powered studies if the total years of diabetes improvement can be maximized with a stepwise approach.

Potentially, sleeve gastrectomy converted to an anastomotic procedure can be more efficacious than what is achieved with the primary anastomotic procedure alone. If some patients are destined for eventual relapse, even after anastomotic procedures, perhaps a stepwise approach would yield a greater number of total years in remission.

The ability of two procedures to surpass the diabetic results of the primary procedure may draw skepticism based off the results we have seen for revisional surgery and obesity. Revisional bariatric surgery has shown variable outcomes with weight loss when compared to the primary procedure. Indeed, in some observational studies, it has yielded lower total weight loss, with inferior durability^[24-26]. However, the same assumptions of inferiority should not be made for the effect of revisional surgery on diabetes. This has yet to be fully evaluated. We know there is not a direct correlation between a patient's weight loss and degree of diabetic improvement and that studies have shown multiple metabolic effects from surgery which are completely independent of weight loss^[7,20]. For example, improvement in glycemic control often occurs prior to any substantial weight loss and the degree of diabetic improvement does not parallel changes in BMI^[6,7,27]. Interestingly, in one sample of 105 gastric bypass patients who had inadequate weight loss (Excess Weight Loss < 15%), substantial glycemic improvement was still observed at one-year follow up (change in mean HbA1C from 7.3 ± 1.9 to 6.1 ± 1.0)^[20]. Additionally, newer studies have theorized several metabolic gastrointestinal modulations caused by surgery that act independent of weight loss. One such observation reveals that increased stimulation to the terminal ileum and large intestine by rapid nutrient delivery (increased gastric emptying or intestinal bypass) appears to have beneficial incretin (GLP-1) secretory effects^[20,27]. Although much research is still underway, it is clear that metabolic and bariatric procedures cause a complex change in gut physiology, with each procedure likely to have its own distinct response. Thus, an approach that combines multiple procedures to target separate pathways may one day be found to be the most efficacious for long-term diabetic improvement.

CONCLUSION

More than a decade of efforts to recognize the incredible glycemic improvement possible with surgery have now provided the foundation for further discoveries. Recently, the cardiovascular benefits from metabolic surgery in obese diabetics have shown dramatic risk reduction in complications such as heart failure, A-fib, stroke, myocardial infarction, and all-cause mortality^[28]. As we continue to recognize additional benefits, further study is needed to continue to guide appropriate procedure/patient selection and to formalize a surgical plan for the long-term care of diabetes.

DECLARATIONS

Authors' contributions

Both authors contributed equally to the entire editorial.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Editorial

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An introduction to the special issue “Small Renal Masses (SRMs): update in diagnosis, management and new ablative modalities”

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Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney and accounts for almost 2% of all cancers. Approximately 270,000 new RCC cases are diagnosed worldwide each year. The highest incidence of RCC is reported in Western countries, with 100,000 new cases per year in Europe. Over the last decades an increase in the detection of localized RCC has been observed, probably due to the widespread use of sectional imaging accounting for incidental diagnosis^[1].

In the 1980s, only 12% of RCC cases were diagnosed as stage T1a and more than 60% accounted for stages T3-4. Currently, almost 60% are stage T1a at diagnosis and locally advanced or primary metastatic renal tumours account for only a quarter of all incidental cases^[2].

The highest incidence of localized tumours or Small Renal Masses (SRMs) is found in the elderly patients, who typically present with a high number of comorbidities. As approximately 70%-90% of these SRMs are malignant RCC, treatment may be required. This has certainly generated great interest in delivering better cancer care for older, more complex patients in a more tailored fashion.

Surgery still represents the standard of care for localized renal cancer. Partial nephrectomy, being open, laparoscopic or robotic has emerged as the treatment of choice for stage T1a-b tumours. Even in the presence of larger tumours, organ preservation can be considered when technically feasible and in select



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patients. The advantages of a nephron-sparing approach are clearly related to renal function preservation guaranteeing consistent oncological outcomes.

Although radical surgical procedures remain the definitive recommended treatment of SRM, non-surgical management or ablative techniques have emerged recently, particularly for smaller tumours (< 4 cm) and for those patients who are not eligible for surgery. Although the overall oncological outcomes are still under evaluation, ablative techniques could theoretically offer the benefit of nephron-sparing treatment with the clear advantages of minimally invasive approaches.

Ablative techniques include cryoablation, radiofrequency ablation, microwave ablation, laser thermal ablation and high-intensity focused ultrasound. Evidence from the literature is more extensive for cryoablation and radiofrequency ablation while the other modalities are still to be considered experimental^[3].

To date, appropriate selection of the best therapeutic option needs to be determined on a case by case basis with thorough patient counseling. There is always a need to find the right balance between the benefits of a given treatment and its risks, without forgetting patients' characteristics.

In this context, ablative modalities seem to be a potentially valid treatment option that can reduce the morbidity and complications related with surgical procedures with acceptable oncologic and functional outcomes.

However, considering the literature, only few series are reporting intermediate - long term survival data and several studies are still evaluating the oncologic efficacy of ablative modalities.

The overall low evidence found in the literature and the lack of standardized techniques are still to be considered as major limitations for these non surgical approaches. Multicentric, randomized high volume trials are typically very complicated to perform in these settings. However, higher quality data from larger series coming from expert centres, focusing on standardization and safety are eagerly awaited for in order to obtain better and comparable oncological outcomes and to allow better reproducibility and teaching of the techniques.

The aim of this review is to focus on the best evidence available on the overall management of SRM highlighting the process from the diagnosis to the non surgical treatment modalities.

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Authors' contributions

Wrote and reviewed the manuscript: Celia A, Naspro R

Availability of data and materials

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Retraction

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Retraction: Diagnostic value of erythrocyte sedimentation rate levels as a predictor of staple-line leakage in bariatric surgery

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This article^[1] has been retracted by authors because there are unresolved issues relating to authorship and contents. All the authors confirmed this retraction.

REFERENCE

1. Kheirvari M, Akbarzadeh I, Eshghjoo S, Yazdannasab M, Alaniz RC, Hosseini S, Anbara T. Diagnostic value of erythrocyte sedimentation rate levels as a predictor of staple-line leakage in bariatric surgery. *Mini-invasive Surg* 2020;4:3.



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Technical Note

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Utility of a lighted stent to avoid male urethral injury in transanal rectal surgery

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Abstract

Total mesorectal excision (TME) is accepted as the standard technique in rectal surgery. In recent years, significant attention has been focused on transanal TME (taTME) as a promising approach for rectal cancer. However, this approach can involve an inherent risk of male urethral injury, because there is no clear anatomical border between the rectal muscularis propria and rectourethral muscle. We used a lighted urethral stent to identify the urethra during taTME for 6 patients with distal rectal cancer. In five of six cases, an infrared-detecting camera could detect a red fluorescent signal from the lighted urethral stent during the anterior dissection of the rectum, which helped us to determine the correct dissection line. A lighted urethral stent is a useful tool that helps visualize the urethra during taTME and improves taTME applicability in clinical practice.

Keywords: Transanal total mesorectal excision, lighted urethral stent, urethral injury

INTRODUCTION

Total mesorectal excision (TME), introduced by Heald, is accepted as the standard technique in rectal surgery^[1]. As compared to open surgery, laparoscopic surgery can provide better visibility in a narrow pelvic space, which enables surgeons to conduct precise TME surgery. Laparoscopic rectal surgery has been accepted based on accumulating evidence; however, it remains technically difficult in cases with obesity and/or a narrow pelvis. Recent randomized controlled trials (RCTs) (i.e., COLOR II and COREAN) exhibited more favorable outcomes of laparoscopic rectal surgery compared with open rectal surgery^[2,3], whereas other recent RCTs (i.e., ALaCaRT and ACOSOG Z6051) did not^[4,5]. In recent years, transanal TME (taTME) surgery for rectal cancer has attracted intense attention due to the improvements in the



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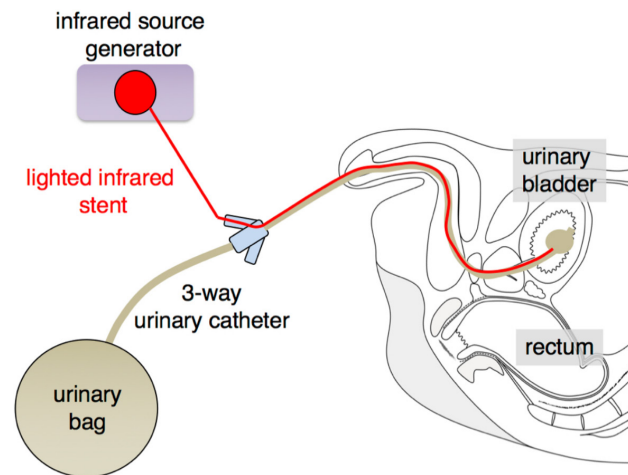


Figure 1. Setup of a lighted stent

quality of TME. However, this approach can involve an inherent risk of male urethral injury during anterior dissection of the rectum^[6-10], because there is no clear anatomical border between the rectal muscularis propria and rectourethral muscle. In taTME surgery, anatomical knowledge of the male anterior anorectum is critical to avoid male urethral injury and rectal perforation. We recently reported the three-dimensional morphology of the male anterior anorectum based on the histological analyses of male cadavers^[11]. In clinical practice, limited studies have reported on the utility of a lighted urethral stent during taTME surgery^[6,7,10]. In this study, we show the anatomical findings of the anterior anorectum in a cadaveric study as well as the availability of a lighted urethral stent in a clinical setting.

METHODS

In a cadaveric study, gelatin-embedded male pelvises were sectioned; the specimens including the anterior anorectum were subsequently dissected for histological examination, as described previously^[11]. Paraffin-embedded serial sections at 10 μ m were used for Elastica van Gieson (EVG) staining and immunohistochemical analysis with antibodies against smooth muscle actin (Smooth Muscle Ab-1, Thermo Fisher Scientific) and skeletal muscle myosin (Skeletal Muscle Ab-2, Thermo Fisher Scientific)^[11]. This study was conducted following the Act on Body Donation for Medical & Dental Education law of Japan.

In a clinical study, we used a lighted stent (Infrared Illumination System, Stryker, Inc.) to identify the urethra during taTME in six patients with distal rectal cancer. For visualization of the urethra, a lighted stent was preoperatively introduced into a three-way urinary catheter (#18Fr Foley), which was placed into the bladder [Figure 1]. The lead of a lighted stent was connected to an external infrared source generator. The wavelength of the lighted stent was approximately 830 nm, and, hence, an infrared-detecting camera system (1588 AIM Platform, Stryker) was employed to detect a fluorescent signal from the lighted stent. Informed consent was obtained from all patients. The study protocols were approved by the Institutional Review Board of Kyoto University.

RESULTS

Figure 2 shows histological sections of the anterior anorectum in the cadaveric study. The urethra was very close to the rectal muscularis propria just inferior to the apex of prostate. In the horizontal section, striated muscle fibers of the puborectalis muscle surrounded the rectal muscularis propria from the anterolateral side to the posterior side. Abundant smooth muscle containing collagen fibers (i.e., rectourethral muscle) extended anteriorly from the longitudinal muscle of the rectal muscularis propria [Figure 2A]. In the

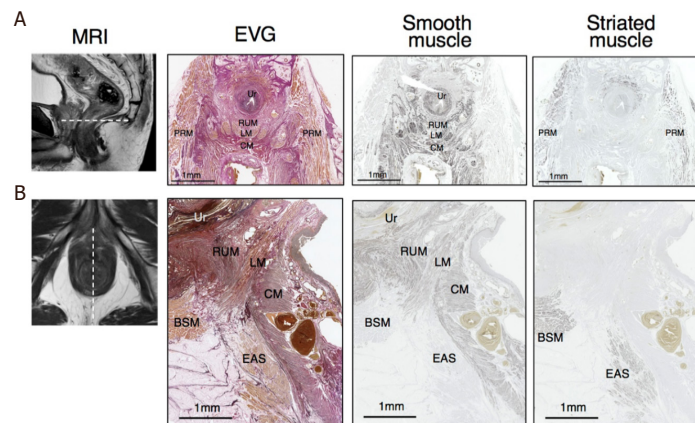


Figure 2. Histological sections. EVG, anti-smooth muscle, and anti-striated muscle staining: (A) horizontal sections; and (B) Sagittal sections. BSM: bulbospongiosus muscle; CM: circular muscle layer; EAS: external anal sphincter; LM: longitudinal muscle layer; PRM: puborectalis muscle; RUM: rectourethral muscle; Ur: urethra; EVG: elastica van gieson; MRI: magnetic resonance imaging

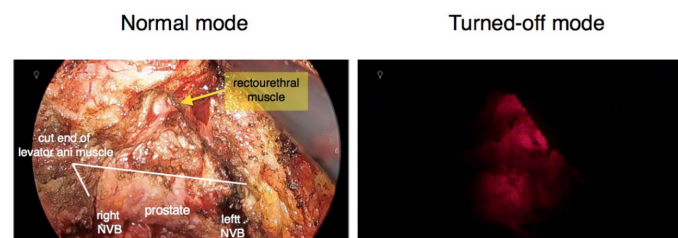


Figure 3. Transanal view of the anterior anorectum in Case 2. Normal mode (left) and turned-off mode (right) are shown. The rectourethral muscle, NVB, and cut end of the levator ani muscle are shown. NVB: neurovascular bundle

sagittal section, the rectourethral muscle occupied the posteroinferior area of the urethra from the upper border of the external anal sphincter muscle to the apex of the prostate [Figure 2B]. There was no clear anatomical border between the rectourethral muscle and longitudinal muscle, indicating that surgeons need to pay attention to urethral injury during division of the rectourethral muscle in taTME.

We used a lighted stent to identify the urethra in six taTME surgeries: abdominoperineal resection (APR; $n = 4$) and intersphincteric resection (ISR; $n = 2$). Vessel ligations and mobilization of the left-sided colon were laparoscopically performed. The perineal approach was conducted under direct vision to attach a GelPoint Mini port device (Applied Medical). After GelPoint Mini was placed, taTME was initiated. The posterior side of the rectum was first dissected until the sacral promontory was reached. Next, the dissection was extended toward the lateral side. Bilateral pelvic splanchnic nerves were preserved at the 5 and 7 o'clock positions. On the anterior side, the correct dissection line could not be easily identified because there was no clear anatomical border. Therefore, an infrared-detecting camera (1588 AIM) was used to detect a red fluorescent signal from a lighted urethral stent in real time during the anterior dissection of the rectum. Figure 3 shows the views of the anterior side in Case 2 (APR). The red fluorescent signal could be detected during division of the rectourethral muscle. The signal was bright with low background under the turned-off mode. Anterior dissection was conducted using fluorescent information as reference. The red-lighted area was located between the superior part of membranous urethra and the inferior lobe of prostate. In five of six cases (i.e., Cases 1-4 and 6), we could detect the red fluorescent signal from a lighted urethral stent under the turned-off mode [Figure 4]. The portion of the lighted area was similar in the five cases, although the fluorescence intensity was slightly different depending on the angle of the lighted stent. Under the normal light mode, the fluorescent signal was not detected in all six cases. In

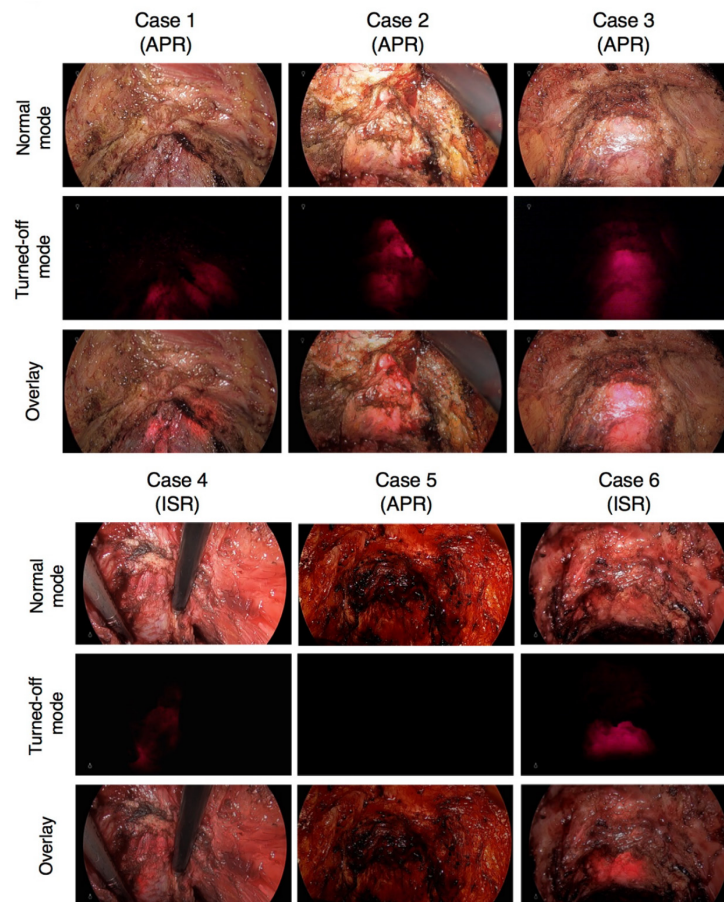


Figure 4. Transanal view of the anterior anorectum in six cases. Normal mode (top), turned-off mode (middle), and overlaid view (bottom) are shown. APR: abdominoperineal resection; ISR: intersphincteric resection

Case 4, the fluorescent signal was weak under the turned-off mode. When the prostate was broadly pressed by the forceps, the fluorescent signal was slightly enhanced. In Case 5, we could not detect a fluorescent signal even if the prostate was broadly pressed. No significant complications were observed in all cases.

DISCUSSION

We previously reported a cadaveric study about the visualization of a lighted urethral stent during transanal ISR^[9]. In the correct dissection plane that resulted in preservation of the urethra, a fluorescent signal was barely identified under the normal light mode, while it could be clearly detected under the turned-off mode. In the incorrect (i.e., deeper) dissection plane that resulted in urethral injury, the lighted urethral stent was clearly detected under both the normal light mode and turned-off mode. Identification of the urethra using the lighted urethral stent under the turned-off mode could be helpful to avoid inadvertent urethral injury during the anterior dissection of the rectum.

In the present study, a fluorescent signal from a lighted urethral stent could not be detected in one case (Case 5). It is not clear why a fluorescent signal could not be detected. Although the lighted stent was designed to illuminate through up to 12 mm tissues, the intensity of the fluorescent signal can be affected by some factors: for example, the thickness of the tissues covering the urethra and prostate, the distance between the lighted stent and laparoscopic camera, the rotation angle of the urinary catheter, and the equipment condition. Further investigation is needed to validate our findings.

CONCLUSION

A lighted urethral stent is useful to visualize the urethra during taTME surgery in clinical practice. The assistance of fluorescent information helped in reducing the risk of urethral injury on the anterior side.

DECLARATIONS

Authors' contributions

Conception and study design: Kawada K, Sakai Y

Data acquisition and interpretation: Kawada K, Okada T

Drafting of manuscript: Kawada K

Critical revision for intellectual content: Okada T, Sakai Y

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

A cadaveric study was conducted following the Act on Body Donation for Medical & Dental Education law of Japan. In a clinical study, informed consent was preoperatively obtained from all patients. This study was conducted in accordance with the ethical principal that have their origins in the Declaration Helsinki, and the protocols were approved by the Institutional Review Board of Kyoto University.

Consent for publication

Not applicable.

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Review

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Pain management following robotic thoracic surgery

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Abstract

For robotic thoracic surgical patients, minimizing pulmonary complications is the key to decreasing morbidity. Once the pain is controlled, the morbidity associated with thoracic surgery is decreased. Consequently, control of pain is the core requirement in robotic thoracic surgical patients. Appropriate pain control depends on a multifaceted program that is based on an understanding of the pathophysiology of pain. A multifaceted pain control program after robotic surgery needs to address local and systemic pain pathways. This review outlines such a multifaceted program with the use of subpleural catheters for prolonged ambulatory infusion of local anesthetic for 10 days, nonsteroidal anti-inflammatory agents, and measured use of narcotic analgesics.

Keywords: Robotic surgery, pain management, analgesia, subpleural catheters, on-Q

INTRODUCTION

Although it is hypothesized that robotic surgery is associated with lower pain-related morbidity, it is important to address pain in the patient undergoing robotic surgery as diligently as a patient undergoing any other thoracic surgical procedure. Unlike the abdomen, even the most minimally invasive procedures on the chest can be painful. In addition, the nature and severity of the thoracic pain experience for each individual patient is highly subjective and complex. Therefore, regardless of the number and type of incisions or ports, acute and chronic pain associated with robotic thoracic surgical procedures should be recognized and treated aggressively.



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For robotic thoracic surgical patients, minimizing pulmonary complications is the key to decreasing morbidity. Studies have shown that simple deep breathing and coughing in the postoperative period can effectively prevent complications such as atelectasis and pneumonia. The ultimate goal is to clear secretions, maintain expansion of the lung, and decrease the complications associated with pulmonary collapse. This goal is achieved by the patient's ability to cough and deep breath, as well as the adjunctive measures of spirometry, chest physiotherapy, and bronchoscopy. In turn, effective clearance of secretions with cough and early mobilization are attained primarily by optimal pain control. Control of pain is the core requirement for all postoperative measures in robotic thoracic surgical patients. Once the pain is controlled, the morbidity associated with thoracic surgery is decreased.

PATHOPHYSIOLOGY OF PAIN

As defined by the International Association for the Study of Pain, pain is both the sensory and the emotional experience that is associated with actual or potential tissue damage, and it is described in terms of that damage^[1]. The unique and individual nature of pain perception stems from the fact that the sensory experience is also associated with an individual's affective and cognitive response. As a result of the complex interaction between the pain stimulant and the individual's unique response to the stimulant, the cause and effect relationship between actual tissue damage and perception of pain is not constant among individuals.

The pain pathway begins with nociception. Nociception is the process whereby certain stimuli (chemical, mechanical, or thermal) activate a specific physiologic neural pathway. Nociceptors are the peripheral nerve endings of sensory neurons and supply skin, muscles, joints, and other tissues. These nerve endings are attached to axons, which communicate with the spinal cord or brainstem nuclei. The faster conducting myelinated axons or A-delta fibers are responsible for the shorter-lived but higher-intensity pain sometimes referred to as "first pain". The slower conducting unmyelinated axons or C fibers produce the duller and more prolonged pain sensation known as "second pain"^[2].

Four processes lead to pain perception: (1) transduction; (2) transmission; (3) modulation; and (4) perception.

(1) Transduction: Transduction takes place in the peripheral nerve endings, where a stimulus is converted to electrical activity.

(2) Transmission: During transmission, the electrical activity is conducted through the nervous system. Axons from peripheral sensory neurons transmit impulses to the spinal cord, where they synapse with second-order neurons. Spinal second-order neurons project to different brainstem and diencephalic structures. In turn, neurons from these structures project to the various cortical sites responsible for sensation.

(3) Modulation: During modulation, the neural input, and thereby the pain process, is altered. Modulation occurs in the dorsal horn of the spinal cord.

(4) Perception: During the phase of perception, the neural activity in a somatosensory pathway results in the subjective sensation of pain. Perception results from the activation of primary and secondary somatosensory and limbic cortices^[3].

With tissue damage, nociceptors are stimulated. The initial stimulation of the nociceptors as the result of tissue damage leads to enhanced response of these receptors and increased sensitivity to further stimuli.

Consequently, stimulated nociceptors are upregulated and become more responsive to further stimuli. Hyperalgesia refers to the phenomenon by which stimulated nociceptors become more sensitive to further stimuli. In addition to upregulation from the original stimulus, several humoral pathways enhance the effect of the painful stimulus. Tissue damage, such as with any incision, releases certain mediators, e.g., bradykinin, potassium, calcitonin gene-related peptide, and prostanoids such as prostaglandins and leukotrienes^[1]. Substance P is also released. Substance P acts on mast cells to induce degranulation with the resultant release of histamine. All these activate and sensitize nociceptors. Substance P also dilates blood vessels, causing edema, and releasing more bradykinin^[4]. Combination of the humoral mediators results in a decrease in the activation threshold and enhances the sensitivity of the nociceptors to further stimuli. In addition, the “cascade” effect results in increased nerve sensitivity over a much wider field than the original injury.

Understanding the peripheral pathways and the chemical mediators is important in devising techniques for pain control. For example, peripheral opioid receptors are uncovered in response to inflammation. These receptors are the target for endogenous opioids, which are released locally by the immune system. Binding these opioid receptors acts to decrease nociceptor output^[2]. Furthermore, it has been shown that a second group of nociceptors are stimulated only by inflammation and serve to increase pain perception after the original tissue damage. Although unrelated to the original stimulus, decreasing inflammation postoperatively helps to minimize the sensitization of these nociceptors.

Two central components in understanding pain in the postoperative patient are peripheral sensitization and central sensitization.

Peripheral sensitization occurs as the result of the pathways outlined in the previous discussion. Once a patient experiences pain, they can have an increased sensitivity to the same stimulus. This results in hyperalgesia. Allodynia results when a previous stimulus that had at one time not caused pain now does. New synapses are formed with dorsal horn cells that previously received nociceptive input and this redistribution allows mechanoreceptors to activate pain pathways by stimuli that are normally non-noxious, such as touch^[5].

There is augmentation of the initial pain response after the peripheral nociceptors synapse with second-order neurons in the dorsal horn of the spinal cord. This is the phenomenon of central sensitization. With repeated stimulation by painful stimuli, the second-order neurons become hyper-responsive and exhibit augmented sensitivity. This phenomenon is referred to as “wind up”. Chemical mediators such as excitatory amino acids glutamate and aspartate at *N*-methyl-*D*-aspartate (NMDA) result in central hypersensitivity. Repeated peripheral stimuli lead to changes in the dorsal horns of the spinal cord or neuroplasticity, which contributes to increased hypersensitivity to peripheral stimuli^[6]. It is hypothesized that the irreversible changes which occur in the dorsal horns of the spinal cord in response to repeated peripheral stimuli may be the cause of chronic pain syndromes.

It is generally accepted that postoperative pain is related to many factors, including the amount of soft tissue injury, resulting inflammation, and rib injury (as in the case of a thoracic surgical procedure). There are other individual factors that need to be considered, including, but not limited to, preoperative tolerance to medications, psychological and social factors, and other co-existing morbidities that may or may not contribute to pain (an example of this is fibromyalgia).

PAIN AFTER ROBOTIC THORACIC SURGERY

Assessment and treatment of the patient undergoing robotic thoracic surgery should utilize the same concepts of peripheral and central sensitization as in any patient experiencing pain after thoracic surgery.

Furthermore, these concepts should be applied to the specific responses of the individual patient. Many studies have focused on the patient undergoing a conventional thoracotomy. It is generally agreed that thoracotomy is an extremely painful procedure that requires aggressive perioperative and postoperative attention to pain management. Any inattention to pain invariably leads to such deleterious consequences as atelectasis, pneumonia, DVT/PE, and subsequently prolonged hospitalization. To minimize complications, it has been hypothesized that decreasing the size of the incision or “sparing” the muscles of the chest will decrease the resulting pain. This commonly accepted hypothesis has not proven to be true. In fact, a recent study by Ochroch *et al.*^[7], 2005, compared patients undergoing a traditional postero-lateral thoracotomy with those undergoing a muscle-sparing thoracotomy and found no difference in perceived pain up to 48 weeks postoperatively.

There has also been recent work outlining the differences between a traditional thoracotomy and a video-assisted surgery. In 1994, Landreneau compared 165 patients who underwent a postero-lateral thoracotomy and 178 who underwent the Video-assisted Thoracic Surgery (VATS) technique. This study found that less subjective pain was reported by the VATS group in the first year after surgery; however, analgesic requirements were similar^[8]. In a smaller study also in 1994, a smaller study reported similar findings comparing the two groups^[8]. However, in this study, the lower levels of perceived pain by the VATS patients was noted only in the first few days after surgery. These studies are substantiated by more recent ones, such as Li *et al.*^[9], 2003, who found that, when compared to the postero-lateral thoracotomy, VATS surgery was associated with significantly less shoulder dysfunction and pain medication requirement in the early postoperative period. While some of the reasons for these differences may be attributed in part to the smaller incisions, which presumably result in smaller amount of tissue injury, the entire reasoning is more complex. Referring to the previous discussion about nociception, it is not only the activation of the nociceptors that leads to hyperalgesia, but also the chemical mediators that are released at the same time and contribute to the overall peripheral sensitization. Yim *et al.*^[10] compared thoracotomy to VATS in relation to cytokine response. They found that not only did the VATS group have significantly less analgesic requirement, but also that plasma levels of interleukin 6 and interleukin 8, both pro-inflammatory cytokines, were reduced in the VATS group. Based on this study, it appears that decreased humoral mediators may contribute to decreased sensitization following VATS. In fact, VATS and thoracotomy may be similar as initial stimuli for nociceptors but the advantage of VATS may be due to the lower level of sensitization and lessened response to the initial stimulus.

As robotic thoracic surgery further decreases the invasiveness of thoracic surgery, the principles of pain management with VATS need to be applied and modified for robotic thoracic surgery.

PAIN MANAGEMENT

Preemptive analgesia

Successful pain management encompasses choices made in both the perioperative and postoperative periods. Earlier pain control may prevent central sensitization. As explained above, beginning pain management earlier will help to prevent central sensitization. There has been much attention paid recently to the concept of preemptive analgesia. Preemptive analgesia is simply the theory that, by stopping or decreasing the input of stimuli (nociception), one can prevent or decrease central sensitization, and, in turn, achieve a decrease in overall pain. An extension to this concept is the hypothesis that, by administering analgesia prior to nociception, it may be possible to decrease chronic pain syndrome. Electrophysiologic data from animal studies have shown that administering low doses of an opioid such as morphine prior to the introduction of a noxious stimulus can suppress spinal cord hyperexcitability. On the other hand, administering that same opioid after the noxious stimulus does not result in the same degree of suppression^[11]. As NMDA is implicated in the “wind up” phenomenon, it is thought that NMDA may play

a role in preemptive analgesia^[11]. Consequently, NMDA antagonists such as ketamine or dextromethorphan are possible agents which may result in preemptive analgesia. However, mostly due to study design and variance in the definition of preemptive analgesia, studies comparing pre-incisional and post-incisional pain control have shown inconsistent results.

The timing of preemptive analgesia has been controversial. In its purest sense, preemptive analgesia is that which is applied prior to any stimulation of the nociceptors by any noxious stimulus. However, studies have defined it as pre-surgical vs. post-surgical administration^[12]. Obviously, anesthesia and its attendant procedures represent noxious stimuli to the patient. Newer concepts of preemptive analgesia are based on the realization that the surgical incision alone does not trigger central sensitization, and that other noxious stimuli such as the inflammatory mediators, ectopic neural activity, and preoperative noxious stimuli may play a significant role in the overall pain experience^[12]. Further studies are required to clarify the appropriate time for preemptive analgesic intervention, which is designed to prevent central sensitization. It is currently unknown what severity or duration of pain is required for sensitization to occur, thus the timing of analgesia is also unknown. Prevention of central sensitization remains the key to a successful strategy for the control of acute and chronic pain.

Options for postoperative pain management

There are several options for pain management in the postoperative robotic thoracic surgical patient. However, the focus of any regimen should be timing and accurate measurement of pain. Early initiation of therapy is paramount to a successful strategy. In addition, since the goal of robotic, or minimally invasive, surgery is early discharge and a quicker recovery, pain management should be compatible with shorter hospitalization and treatment in the outpatient setting.

Under-treatment of pain remains a problem in both hospital and outpatient settings. A multi-center survey showed that, although patients' satisfaction with pain management had improved from 14% to 19%, as many as eight out of ten patients reported inadequate pain management^[13]. This study showed that mobility improved with better pain control^[13].

Assessment of pain needs to be accurate and consistent. Although there are many proven approaches, there remains a shortage of knowledge and a lack in consistency and follow-through. Use of a pain scale has been shown to provide a clear method for evaluating and tracking postoperative pain. The visual analog scale has been shown to be an effective tool for measuring surgical pain. Furthermore, it has been shown to be an excellent tool for comparing pain levels between groups at a point in time or to track a single patient's pain and response to interventions^[14,15]. The intensity of pain should be recorded and reviewed at regular intervals as well as after each intervention, and the same measurement scale for pain should be used across all disciplines, from anesthesia to the bedside nurse.

Systemic pain control

Opioid administration

Until recently, opioids have been the mainstay of analgesia in the postoperative robotic surgery patient. They have proven value in managing severe pain. Opioid administration begins intravenously in the perioperative period. It usually continues via intravenous methods until the patient is awake and able to take a diet without difficulty. This can take up to a day depending on the patient's reaction to anesthesia, timing of the surgery, and individual pain perception. Patient controlled analgesia (PCA) is an accepted route of intravenous (IV) opioid administration. It has a high acceptance level among patients and allows for quick and easy administration. However, this technique is not always necessary in the patient undergoing minimally invasive surgery and should be considered on an individual basis. Intravenous opioids should be converted to the oral route as soon as possible. While intravenous opioids have rapid

onset, they also have shortened duration of action and prolonged use can lead to a “roller coaster” effect of pain followed by relief of pain. Opioids are associated with significant side effects: nausea, vomiting, respiratory compromise, and ileus. Consequently, they are used in a manner which can result in ineffective pain control.

Oral administration is reserved for when the patient can take a diet without difficulty. Transitioning smoothly to an oral regimen is key. A shortcoming of the oral route is the delay in the onset and peak of drug activity. The addition of a long acting opioid will aid in preventing this “peak and valley” phenomenon.

The use of opioids may extend for several days to several weeks and is highly patient dependent. Many practitioners are hesitant to prescribe opioids long term for several reasons. The treatment of pain with opioids and the prevention of the side effects is preferable to the consequences associated with poor pain control, usually stated as side effects of nausea and constipation as well as fear of addiction. All prescribers of opioids have an ethical duty to provide appropriate pain relief to their patients, while taking into account the many societal and political issues that have emerged as the result of opioid over prescription. Obviously, opioids need to represent an adjunct to a more effective pain management strategy.

Nonsteroidal anti-inflammatory agents

Inflammation is a natural and often protective response to tissue injury caused by surgery. It usually subsides when healing is complete. Inflammation is triggered by the release of chemical mediators, which progress with a cascade effect. Prostaglandins are key mediators in the process of nociception. Prostaglandins are synthesized in the spinal cord and are produced from arachidonic acid via the cyclooxygenase pathway. There are two defined and a third as yet undefined cyclooxygenase enzymes^[2]. COX-1 is in most cells as well as the peripheral and central nervous systems and is produced a number of pathways. COX-2 is generated to a more limited extent, mostly in the central nervous system. Inhibiting the COX enzyme and thereby decreasing peripheral and central prostaglandin production has been shown: (1) to decrease the inflammation associated with tissue injury; and (2) to decrease peripheral and central sensitization. Zhu and Eisenach^[16] demonstrated that there are differences in spinal COX isoenzymes involved in different pain states, with a dominant role for spinal COX-2 with peripheral inflammation and a more exclusive role for COX-1 after incisional surgery. This may have implications for control of hypersensitivity after nerve injury but needs to be shown in humans.

Postoperative use of NSAIDs has been shown to decrease opioid use while still providing adequate analgesia. Furthermore, NSAIDs have little effect on hemodynamic parameters, with negligible changes in blood pressure and stroke volume. In addition, in comparison to opioids such as morphine, which has been shown to decrease minute ventilation and increase pulmonary vasoconstriction, NSAIDs have very little effect on pulmonary circulation^[2].

The use of NSAIDs may impact renal function. This is especially relevant in thoracic surgical patients who are usually elderly and are subjected to postoperative fluid restriction. However, several studies have not supported this hypothesis. In patients with normal preoperative renal function undergoing thoracic surgery, the use of NSAID was associated with minimal reduction in creatinine clearance and no change in urine output^[2]. Another concern is the potential for gastrointestinal bleeding associated with NSAID use. While gastrointestinal erosion can be seen with long-term or chronic NSAID use, its incidence has not been proven with short-term perioperative use. However, several studies have shown that, for long-term use, COX-2 inhibitors may be superior to non-selective NSAID^[2].

Ketorolac (Toradol), 15 mg every 6 h (can be intravenously or intramuscularly), is typically the NSAID used in the perioperative period. The intravenous route is a preferred route in the immediate postoperative

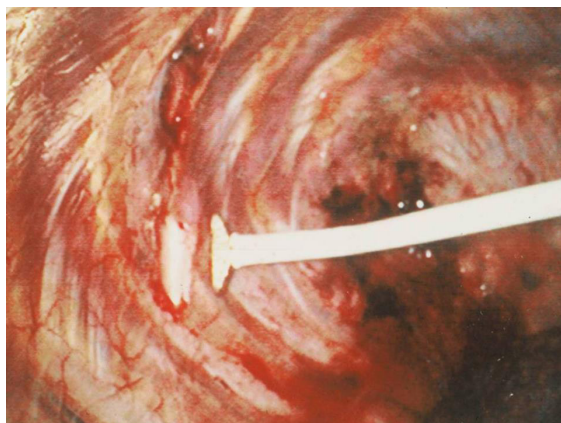


Figure 1. View of the right pleural space. Cryoanalgesia probe being used to freeze the intercostals nerve

period. In addition, ibuprofen, 400-600 mg every 6-8 h, and indomethacin, 25 mg every 8 h, are used. COX-2 inhibitors are less available due to recent studies showing a potential increased rate of cardiovascular thromboembolic events.

Local pain control

Several strategies have been used for local pain control in thoracic surgical patients.

Epidural analgesia

Epidural analgesia is a generally accepted form of analgesia in patients undergoing a thoracotomy. The catheter is normally left in place for three or four days. Epidural catheters require constant attention. A percentage of the catheters malfunction and require removal versus replacement. Patients are generally not allowed to bathe or shower until the catheter is removed. Complications include neurologic injury and bleeding around the spinal cord. Hypotension and urinary retention are common side effects^[17]. Although epidural catheters can provide excellent pain relief, they are not commonly used with VATS because of the time required for insertion, frequent side effects, and the relatively short period of effective use^[18,19]. Earlier ambulation and shorter hospital stay with VATS and robotic thoracic surgery preclude the use of epidural catheter.

Cryoanalgesia

In 1999, Detterbeck *et al.*^[19] showed a decrease in perceived pain in patients undergoing VATS surgery with cryotherapy of the intercostal nerves when compared to those undergoing VATS and pain management by epidural catheters and analgesics. In a subsequent study, cryoanalgesia of the intercostal nerves was shown to be effective in preventing post thoracotomy pain syndrome in patients who had undergone VATS^[20] [Figures 1 and 2]. However, several studies have shown that cryoanalgesia is associated with long-term complications. Most notably, cryoanalgesia has been associated with long-term neuralgia in the distribution of the treated nerves in up to 12% of patients^[20,21]. Although cryoanalgesia was associated with excellent short- and long-term pain control following VATS, it was associated with irreversible hyperesthesia in 8% of patients. It has been hypothesized that this was due to the inability to control the degree and depth of the cold injury to the nerve, which resulted in irreversible damage and neuralgia^[22,23]. As a result of this experience, intercostal cryoanalgesia is no longer used in thoracic surgical patients.

Paravertebral blocks

Intraoperative paravertebral (subpleural and intercostal) administration of long-acting local anesthetic agents have been used. This technique uses individual intercostal blocks or placement of an indwelling

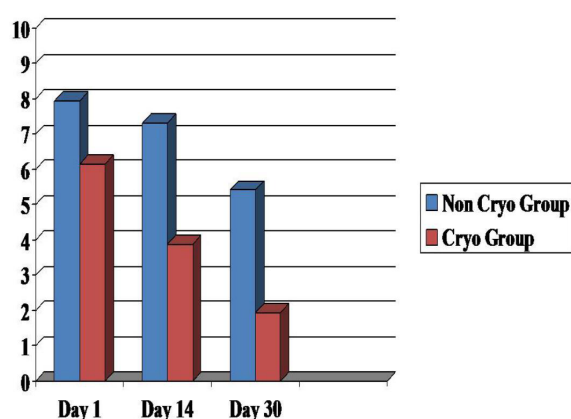


Figure 2. Comparison of cryoanalgesia with conventional pain control techniques utilizing Likert Pain Scores. Although the level of the pain is significant, cryoanalgesia is more effective than conventional pain control techniques in controlling pain on Days 1, 14, and 30

catheter. The blocks generally last 18-24 h and are very effective and considered by some equivalent to an epidural in the first 24 h^[24]. A major shortcoming of this technique is the variability of catheter or block placement by different practitioners, the extra time required in the operating room, and the inconsistent results from errors in catheter placement.

Liposomal bupivacaine

Standard bupivacaine maintains local anesthetic effects for approximately 18 h. Liposomal bupivacaine (Exparel) has prolonged local anesthetic effect for up to 72 h. Liposomal bupivacaine is administered using either a transcutaneous or a intrathoracic technique. Liposomal bupivacaine is approved for local administration in surgical incisions; however, many thoracic surgeons are using this medication for subpleural paravertebral blocks in an off-label application. Using this technique, pain relief has been shown to be better than shorter-acting agents and similar to thoracic epidural^[24,25]. In addition, studies have shown decreased postoperative narcotic administration, shorter hospital stays, and better pain scores versus thoracic epidural analgesia^[26-29].

Subpleural infusion of local anesthetic

Presently, most robotic surgeons begin the procedure with infiltration of the intercostal nerve with local anesthetic prior to the conduct of the operation. Other surgeons use local infiltration of the intercostals at the end of the procedure as their preferred method of local pain control. One shortcoming of this technique is that the local pain control is short lived and the effect of the local anesthetic quickly wears off.

On the other hand, multiple studies have shown that the continuous infusion of local anesthetic through a catheter placed in an extra pleural tunnel overlying the intercostal nerves to be safe and efficacious^[30]. The advantage of this technique is prolonged local pain control. Some investigators have reported placing the catheter in an extrapleural pocket, while others have placed them close to the heads of the ribs in the paravertebral space^[30]. Various types of catheters have been used. Randomized studies have demonstrated better pain relief, better pulmonary function, lower pulmonary complications, and lower use of narcotics with the use of extrapleural infusion catheters^[31-34]. Studies are bearing out the efficacy of subpleural infusion of local anesthetic in the acute setting. Taylor *et al.*^[33] specifically studied the use of this technique in minimally invasive surgery and found it to be an effective form of analgesia and to decrease narcotic requirements postoperatively. In addition, Concha *et al.*^[34] studied the use of intercostal nerve blockade combined with IV PCA compared to epidural analgesia and found little statistical significance between the two groups. Detterbeck reviewed studies on extrapleural catheter use in patients undergoing



Figure 3. Tunneler for subpleural placement of local anesthetic catheters

thoracotomy and found that the use of extrapleural catheter for analgesia was superior to systemic narcotics^[30]. In addition, the use of extrapleural catheters resulted in lower narcotic consumption and decreased pulmonary complications. DiMaio *et al.*^[35] compared the use of a local infusion of an anesthetic to an epidural catheter and found not only improved pain and decreased narcotic usage, but also improved pulmonary function, as demonstrated by an increase in lung volumes. Choice of local anesthetic is surgeon dependent. Moreover, the above-mentioned review did not find a difference in pain relief or postoperative complications when comparing bupivacaine, lidocaine, and lignocaine^[30]. Complications related to the catheter and the local anesthetic agents are low. Reported complications have been less than 0.6% and have included: transient hypotension, transient Horner's syndrome from placement of catheters above the third intercostal space, transient ipsilateral femoral nerve dysfunction from placement of catheters lower than the eighth intercostal space and infusion of the local anesthetic into the retroperitoneum, bupivacaine toxicity in the form of confusion, transient elevation of liver enzymes, and rib osteomyelitis^[30].

Technique for the placement of subpleural catheters after robotic surgery. <https://youtu.be/2JaF3j4re40>; <https://youtu.be/b49GXgEmyZM>

The video of this technique can be accessed using the above links. Although several techniques have been described, we have devised a rapid and reproducible technique for the extrapleural placement of the catheters. With this technique, two soaker catheters are inserted through a subpleural tunnel that extends from the second to the eighth intercostal spaces and encompasses the area of the trocars.

Following the completion of the robotic procedure and undocking of the robot, the camera trocar is removed. An endoscopic camera (Olympus Endoeye 0 Degree) is introduced through the anterior port and used to visualize the paravertebral pleura. In this technique, a specially designed tunneling device is introduced through the camera port and used to begin the formation of a subpleural tunnel. After the formation of the tunnel, the metal tunneling device is withdrawn and a peelable sheath is positioned over the tunneler and replaced in the pleural tunnel. The metal tunneler is withdrawn and the sheath is left in place inside the pleural tunnel. Two five-inch on-Q soaker catheters are introduced through separate puncture sites placed anteriorly in the same intercostal space as the inferior incision [Figure 3]. The on-Q soaker catheters are passed into the long subpleural sheath, and then the sheath is withdrawn and peeled away, leaving the soaker catheters in the subpleural tunnel. The catheters are positioned in an overlapping staggered manner to provide infusion of the local anesthetic for the entirety of the pleural tunnel extending from the second to the eighth intercostal spaces. We use the on-Q Pain Buster soaker catheters (I-Flow Corporation, Lake Forest, CA), which are small flexible catheters with multiple side holes that can deliver

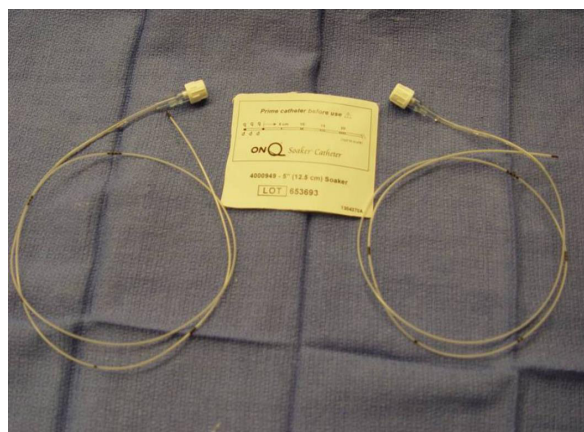


Figure 4. Five-inch on-Q soaker catheters



Figure 5. (A-E) Steps for the placement of subpleural catheters for local infiltration of local anesthetic for 10 days in the ambulatory setting

the infusion over multiple areas [Figures 4-6]. With the on-Q system, flow rate and duration are dependent upon the model used, and can range from 0.5 to 10 mL/h with a reservoir volume of 65-400 mL. For robotic thoracic surgery applications, we use two catheters, an infusion of approximately 4 mL/h (2 mL per catheter) with a 400 mL reservoir and 0.125 bupivacaine. This system is used after the patient is discharged from the hospital, giving the patient 10 days of local pain control. In our institution, intercostal nerve blockade by infusion of a local anesthetic via a subpleural catheter has been shown to be an effective alternative to epidural catheters and cryoanalgesia. This technique provides excellent prolonged pain control after robotic thoracic surgery while decreasing the need for narcotics [Table 1]^[36].



Figure 6. On-Q catheters in place in the narrow subpleural tunnel

Table 1. Likert Pain Scores Median (Range), Subpleural local anesthetic (*n* = 243) vs. Epidural catheter supplemented by narcotics (*n* = 238)

	Day 1	Day 14	Day 30
Epidural	8 (4-9)	7 (5-9-8)	5 (1-5)
Subpleural Catheter	2 (1-3)	1 (1-3)	1 (0-1)
	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001

CONCLUSION

A combined, multimodal approach appears to be the most effective one in dealing with analgesia in the thoracic surgical patient. Any treatment modality needs to attempt to decrease the overall pain experience by preventing sensitization at any time throughout the perioperative course. Thus, multimodal therapy means focusing on addressing pain at the various sites. A multimodal program may embrace two or more therapies. For example, use of neural blockade, whether by epidural or other nerve blocks, is combined with systemic opioid administration (first intravenously, and then via oral route). In addition, NSAID use such as ketorolac in either the preoperative or postoperative phase can also add to the multimodal effect. Choice of a modality is dependent upon many factors, including surgeon preference, anesthesia preference, institutional features or limitations, and personal success or failures with certain treatments. Regardless, a comprehensive pain management regimen is essential for any robotic thoracic surgical program.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

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Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Thoracic surgery by minimally invasion robot-assisted in children: “experience and current status”

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Abstract

Aim: We report our experience in minimally invasive thoracic robot-assisted surgery in children, and a current analysis is carried out on this topic.

Methods: Observational, prospective, and longitudinal studies were performed for children with thoracic pathology treated with robotic surgery, from March 2015 to April 2019. We used the “da Vinci surgical system” (Intuitive Surgical, Inc., Sunnyvale, CA. USA). Registered variables included demographic data, diagnosis, surgery, total time, time of console surgery, bleeding, hemotransfusions, conversions, complications, postoperative (PO) stay, and follow-up. Measures of central tendency were used. Research Ethics Committee of Hospital approved the study. We conducted a detailed non-systematic review of previous publications of children undergoing thoracic robotic surgery.

Results: We treated 11 children, with average age of 5.7 years and weight of 21.3 kg. Diagnosis were: congenital cystic adenomatoid malformation, intralobar sequestration, diaphragmatic paralysis, diaphragmatic eventration, mediastinal teratoma, Ewing’s tumor of the fourth left rib, and pulmonary tuberculosis. Surgeries performed were: four lobectomies, four diaphragmatic plications, two tumor resections, and a case of pleural and lung biopsies. The average of console surgery time was 166.45 min, PO stay was 3.6 days, and follow-up was 24.7 months. Conversions and PO complications were 9.1%, and there were no intraoperative complications and mortality. Currently, the number of children treated with thoracic robot-assisted surgery has barely reached 100 cases.



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Conclusion: Our results are encouraging, although our experience is limited to a few cases. Robotic surgery for the treatment of thoracic pathology is feasible and safe, and has advantages. To date, very few patients have been treated, and few pediatric surgeons worldwide have applied thoracic robotic surgery in children.

Keywords: Robotic surgery, thoracic surgery, thoracic robotic surgery, thoracoscopy, congenital malformations, children

INTRODUCTION

Minimally invasive techniques are applicable in more than 60% of abdominal and thoracic operations in children, according to evidence-based data and ethical principles can be used properly^[1]. The first publication on thoracoscopy in children dates from 1971 in Russia and, fundamentally its application at that time was diagnosed in thoracic diseases and neoplasms^[2]. From that date to the present, thoracoscopic surgery in children has been applied in a wide range of thoracic pathologies, with diagnostic and therapeutic procedures.

The global experience in thoracoscopic surgery in children is more than 30 years compared to robot-assisted thoracic surgery (RATS), and, although the learning curve for thoracoscopy is longer compared to RATS, there are centers in the world where this curve has been overcome. The minimally invasive surgical (MIS) approach offers obvious advantages over the open technique to solve various thoracic pathologies^[3]. In 1981, Rodgers reported 80 thoracoscopic procedures in children, which were performed without mortality and with minimal morbidity, and the main technique was lung biopsy^[4].

An important aspect in pediatric age is to prevent or avoid sequelae of surgery. Makita *et al.*^[5] conducted a comparative study to identify risk factors for thoracic and spinal deformities (scoliosis, pectus excavatum, chest asymmetry, and pectus carinatum) after lung resection during childhood, in patients undergoing thoracoscopic surgery versus thoracotomy. Their results are as follows: nine deformities ($n = 49$) were observed during follow-up in patients with thoracoscopy (18.3%), while patients with thoracotomy reported 19 deformities ($n = 25$) (76%), with a P value of 0.000022. The authors concluded that minimally invasive thoracic surgery (MITS) reduced the risk of thoracic and spinal deformities after lung resection in children.

The most commonly performed technique in children with thoracoscopic surgery is lobectomy, but the learning curve is prolonged. An analysis of the learning curve in pediatric thoracoscopic lobectomy for congenital pulmonary malformations required a minimum of 50 cases of experience to obtain stable results with video-assisted thoracic surgery in pulmonary resections^[6]. This factor is one of the key obstacles for the thoracoscopic technique to be applied more widely in the world in the pediatric population.

With the learning curve overcome, meticulous thoracoscopic lobectomy is feasible in children, and it is effective in avoiding common postoperative (PO) complications, accelerating the recovery, and shortening the hospitalization time^[7].

Clermidi *et al.*^[8] published a study evaluating the feasibility of a fast-track protocol in thoracoscopic lung resection for congenital pulmonary airway malformations (CPAM) in children in 2017. Through the three periods, median PO hospital stay decreased (four, three, and two days, successively; $P = 0.02$). In the third period, four patients underwent day-case surgery. The authors concluded that the fast-track protocol for children undergoing uncomplicated thoracic surgery for CPAM seems feasible without extra morbidity, and selected patients undergoing thoracoscopic resection may benefit from the absence of pleural tube and can be operated on in day-case surgery.

In the adult population, Melfi *et al.*^[9] published the first report on robotic surgery for thoracic diseases, with encouraging results in their preliminary experience. They believed that robotic procedures are technically feasible. Theirs was the first robotic lobectomy in Europe (February 2001, and published in 2002).

In the United States, the first pulmonary lobectomy performed with robotic assistance was reported in July 2003, in a 48-year-old woman with lung cancer^[10].

The first publication on pulmonary lobectomy with robotic assistance, including pediatric cases, is from Park *et al.*^[11], in 2006. They concluded that RATS lobectomy is feasible and safe, and the usefulness and advantages of robotic assistance for lobectomy require further refinement and study of the technique.

Toker^[12] and his group started with a thoracic robotics program after an established experience of video-assisted thoracic surgery (VATS). The idea for a thoracic robotic program was based on the anatomical difficulties of some thoracoscopic lung resections and the superior capabilities of the robotic articulated instruments.

The main advantages of using a robotic device are: (1) the precision of the instrument and improved dexterity due to the use of “wristed” instruments; (2) three-dimensional imaging, with improved ability to locate blood vessels, nerves, and tissues; and (3) the surgeon’s console, which reduces fatigue and allows for tremor-free manipulation^[13].

The improvements with robotic assistance offer technical capabilities beyond the existing threshold limits of human performance for surgery within restricted work spaces in children; the camera is controlled by the primary surgeon; and articulated instruments allow dissection and precise anastomosis^[14]. The above are advantages for the surgeon, which benefit the patient.

RATS is gaining more acceptance for the adult population and recently large series have been reported on lobectomy^[15,16] and excision of the mediastinal cyst^[17].

The first robotic procedure in children was fundoplication, and was carried out by Meininger *et al.*^[18] in July 2000 and reported in 2001.

The safety of robotic-assisted surgery in children is reported to be similar to open procedures, and the outcomes are at least equivalent to standard laparoscopy^[19].

Very few cases of RATS have been reported in children. The first publications of RATS in children were in the area of cardiovascular surgery^[20,21].

Ballouhey *et al.*^[22], in 2015, published on 11 patients treated with RATS at two pediatric surgery centers over a period of six years. Their conclusions were RATS for newborns and infants is still very challenging; these patients are not good candidates for this approach; and the most appropriate procedures are the removal of mediastinal cysts in children weighing more than 20 kg.

The objective of this article is to inform about our experience in MITS assisted by robot in children. In addition, a current analysis is carried out on this topic.

METHODS

Observational, prospective, and longitudinal studies were performed for pediatric patients with thoracic pathologic treated with RATS, from March 2015 to April 2019. The diagnosis was made with laboratory

studies, X-rays, ultrasound, CT scan image, angiographic study, and histopathology, according to the patient.

The surgeries were performed by MITS assisted by robot. We used the “da Vinci surgical system Version Si” (Intuitive Surgical, Inc., Sunnyvale, CA. USA).

We use four or five trocars (three of four robotics and one laparoscopic). To collapse the hemithorax lung to operate, in patients younger than six years, we used CO₂ at 6 mmHg of pressure and flow of 1-4 liters per minute, while, in patients older than six years, selective intubation of the contralateral bronchus was used.

Registered variables included demographic data, diagnosis, surgical technique, total time, time of console surgery, bleeding, hemotransfusions, conversions, complications, PO stay, and follow-up. The data were entered into a spreadsheet in Microsoft Office Excel 2013.

Seven cases are part of the statistics of our published series of the first three years of robotic surgery^[23].

Measures of central tendency were used. In relation to ethical considerations of the study, being of an observational nature, it was not necessary to obtain the informed consent for the patients to enter the study. The Research Ethics Committee of the Hospital evaluated and approved the study. To perform the medical and surgical procedures, we obtained the informed consent in writing from the parents or guardians.

We carried out a detailed non-systematic review of previous publications in PubMed on thoracic pathology treated with robotic surgery in the pediatric population, with the following four search strategies (at: <https://www.ncbi.nlm.nih.gov/pubmed/>): (1) robot-assisted thoracoscopic surgery + thoracic robotic surgery + children; (2) robot-assisted thoracoscopic surgery + children; (3) thoracoscopic robotic surgery + children; and (4) robotic surgery thoracic + children.

RESULTS

We treated 11 patients with thoracic pathology, six male and five female. The average age was 5.7 years (range 6 months to 15 years), the average weight was 21.34 kg (range: 5.93-60 kg), and the average height was 107 cm (range: 66-176 cm). The diagnoses were three congenital cystic adenomatoid malformation (CCAM) and an intralobar sequestration; three right diaphragmatic paralysis and a diaphragmatic eventration; and one case each of mediastinal teratoma, Ewing's tumor of the fourth left rib, and pulmonary tuberculosis. The surgeries performed were: four lobectomies (36.36%), four diaphragmatic plications (36.36%), two tumor resections (18.2%), and one pleural and lung biopsies (9.1%).

The following average values were found: console surgery time, 166.45 min (range: 25-314 min); bleeding, 42.27 mL (range: 0-150 mL); and PO stay, 3.6 days (range: 1-12 days). Conversions and PO complications were reported in one patient, and there were no intraoperative (IO) complications and mortality. Hemotransfusions were reported in one patient: a 10-month-old girl, weighing 5.93 kg and 66 cm tall, who entered the operating room with low hemoglobin, the diagnosis of CCAM, and underwent lower right lobectomy. She required 314 min of console surgery time, presented 40 mL of bleeding, and was hemotransfused in the immediate PO period. Her PO stay was three days. This is our smallest patient by weight and height.

The patient with Ewing's tumor, from the left hemithorax, was a seven-year-old boy, weighing 21 kg and was 102 cm tall. The patient initially underwent an open incisional biopsy, through a 5-cm incision over the tumor area, obtaining the histopathological diagnosis of Ewing's tumor of the anterior arch of the

fourth left rib, with pulmonary invasion. After the favorable evolution with the cancer medical treatment and that the tumor could be resectable, a second surgery was planned for block resection, as follows: (1) RATS performed a non-anatomical segmentectomy, using staplers, resection with a healthy pleura flap, and tumor with 4 cm of the fourth left rib (using a Gigli saw); (2) before dedocking, an open resection of the overlying soft tissues was performed, including the 5-cm-long scar, and then the closure of the chest wall; and (3) using RATS, a mesh was applied to stabilize the chest wall, concluding surgery. The surgical time of the console was 240 min and there was 60 mL of bleeding. The pleural tube was left, which was removed on the second day of PO.

The conversion was a lobectomy in a 10-month-old boy weighing 7.8 kg, with a diagnosis of right basal intralobar pulmonary sequestration due to technical difficulties. The PO complication was the prolonged drainage of serous fluid, in an eight-month-old girl weighing 8 kg, who underwent a diaphragmatic plication due to the diagnosis of diaphragmatic paralysis. The pleural drainage was removed on the eleventh day and was discharged daily; this complication is of grade I, according to the classification of Clavien *et al.*^[24]. The average follow-up was 24.7 months, ranging from 9 to 51 months.

We performed a detailed non-systematic review of previous publications in PubMed on the thoracic pathology treated with robotic surgery in the pediatric population. We obtained 4, 8, 30, and 50 publications, respectively, using the four search strategies, but only 15 publications were about our topic. Currently, the number of children with non-cardiovascular thoracic pathology treated with robotic surgery has barely reached 100 cases.

DISCUSSION

We present a series of 11 RATS. These data support that some robotic procedures are surgically feasible. Our study and others confirm the technical advantages of thoracic robotic surgery, such as precise dissection and suturing in very small spaces^[20,22], in addition to its general advantages, such as stereoscopic and magnified vision, in 3D, scale movements, tremor filtration, and the surgeon's console for operating while sitting and with total ergonomics. In addition, the articulated instruments are superior to the rigid thoracoscopic instruments in the thoracic cavity, which itself is quite rigid^[22].

During the same period of this study, we performed a total of 254 robotic procedures in pediatric patients, with eight conversions to open surgery. RATS corresponds to 4.3% of the total procedures in our experience.

The first publications of RATS in children were about cardiovascular techniques, such as patent ductus arteriosus (PDA) closure and vascular ring division^[20,25]. In the 2000 study by Le Bret *et al.*^[20], 56 children underwent a surgical closure of a PDA, 28 patients with thoracoscopic technique and 28 with a robot-assisted approach. They used the ZEUS robot surgical system (Computer Motion, Inc., Goleta, CA, USA), concluding that the robotically assisted closure of a PDA is comparable with closure by means of the thoracoscopic technique. However, robot-assisted approach required a longer operative time because of the increment in complexity. Previously, starting in 1991, these authors had performed 630 procedures of thoracoscopic closure of the PDA, and their first 28 surgeries with a robotic approach. Based on the above, robotic assistance offers advantages and with few procedures the results are similar to the thoracoscopic technique.

Currently, very few cases of RATS have been published. However, many studies have reported that robot-assisted surgery is safe and feasible for pediatric patients.

Table 1. Comparative series of cases of thoracic robotic surgery in children

	Sandler and Meehan ^[27] (2008)		Ballouhey <i>et al.</i> ^[22] (2015)		Current data	
Cases	11		11		11	
Gender (male/female)	?		4/7		6/5	
Age	?		72 months (0-204)		68.4 months (6-180)	
Weight	?		24.4 kg (3-51.5)		21.34 kg (7.8-60)	
Diagnostics	Posterior mediastinal mass	2	Oesophageal atresia	3	CCAM	3
	CCAM	2	Bronchogenic cyst	3	Diaphragmatic paralysis	3
	Mediastinal germ cell tumor	1	Diaphragmatic hernia	2	Intralobar sequestration	1
	Mediastinal teratoma	1	Oesophageal duplication	1	Diaphragmatic eventration	1
	Mediastinal inflammatory mass	1	Gastric tube/oesophagoplasty	1	Mediastinal teratoma	1
	Bronchogenic cyst	1	Acalasia	1	Ewing's tumor	1
	Intralobar sequestration	1			Pulmonary tuberculosis	1
	Pulmonary segmentectomy	1				
	Congenital diaphragmatic hernia	1				
Surgeries	Resection of tumor masses	6	Correction oesophageal atresia	3	Lobectomy	4
	Lobectomy	3	Bronchogenic cysts resection	3	Diaphragmatic plication	4
	Segmentectomy	1	Diaphragmatic plasty	2	Tumor resection	2
	Diaphragmatic plasty	1	Oesophageal duplication resection	1	Pleural and lung biopsies	1
			Gastric tube/oesophagoplasty	1		
			Heller myotomy	1		
Conversions	2 (18.2%)		3 (27.3 %)		1 (9.1%)	
Surgical time	?		190 min (120-310)		166.4 min (24-314)	
IO complications	0%		0%		0%	
PO complications	0%		2 (18.2%)		1 (9.1%)	
PO stay days	?		13.5 days (3-35)		3.6 days (1-12)	
Follow-up	?		26.9 months (8-55)		24.7 months (9-51)	

CCAM: congenital cystic adenomatoid malformation; IO: intraoperative; PO: postoperative

RATS has previously been described as part of a series of general pediatric surgeries or a series of various thoracic pathologies^[22,23,26,27], a series of pediatric cases of specific procedures such as thymectomy for myasthenia gravis^[28,29], tracheopexy for treatment of severe tracheomalacia^[30], or as pediatric case reports on esophageal leiomyoma and bronchogenic cyst^[31-33].

We compared the results of two published series with ours^[22,27]. The three series are comparable, due to the diversity of thoracic pathologies and procedures and the number of cases of RATS in children. In our series, there was less conversion, less surgical time, less PO complications, and fewer days of PO stay. Conversion was more frequent in patients with lower weight, especially in newborns [Table 1]. Most conversions in RATS are in children weighing less than 5 kg, and the extreme limit is 2.5 kg^[22].

Patients between 3 and 5 kg with RATS are a great challenge and require experienced and capable surgeons. The fundamental technical limitation and disadvantage of RATS is in newborn patients and patients weighing less than 3 kg.

The dimensions of the robotic instruments (8 mm) require a minimum critical space to be manipulated, i.e., 5 mm. Their limitations are that they require more interior space in the cavity and have no energy. In the future, it will be necessary to implement a greater miniaturization of technology, preserving the functionality to treat children with lower weight.

The docking charts for robotic surgery suggested for surgical techniques in adults are not applicable for children. Therefore, sometimes, 3 cm of separation was required between each trocar when surgery was performed on infants, due to limited space in such small patients^[23].

Cundy *et al.*^[34] conducted a systematic search in the literature of reported cases of robotic surgery in children over a period of 11 years. They included 137 articles, with 2393 procedures in 1840 patients, and thoracic procedures accounted for 3.2% (77 surgeries and 12 different techniques). The conversion rate was 10% in RATS. The results show that the five most frequent RATS procedures are: lobectomy^[18], thymectomy^[14], benign mass excision^[9], diaphragmatic plasties^[8], and resection of malignant tumors^[5]. The other areas and procedures of robotic surgery that were part of this research were urological procedures (1434, 59.9%) and gastrointestinal procedures (882, 36.9%). Our small series of RATS cases coincides with the aforementioned data, in terms of thoracic pathology, surgical techniques, and conversion rate [Table 1].

Lobectomy is the most reported RATS, thus it is important discuss the surgical technique in children: (1) it is essential to have an excellent pediatric anesthesiologist, for the management of ventilation with a single lung, either by selective intubation (school-aged children and teenagers), or using 6 mmHg of pressure with CO₂ for pulmonary collapse; (2) for school-aged patients and adolescents, there should be an assistant surgeon who has the skills to handle and apply staplers, as it is the safest way to manage vascular structures, bronchial tubes, and interlobar lung tissue.

In most of our RATS procedures, from the open technique we jump to robotic surgery, due to the low frequency of presentation of these pathologies, and the thoracoscopic technique implies a longer learning curve. This also happened to Meehan and Sandler^[27]. Robotic assistance is ideal for complex hepatobiliary cases and thoracic surgery, particularly for solid mass resection^[35,36].

Despite performing several different types of operations in the first months, we felt comfortable with the robot after approximately 15 cases. This experience is consistent with our colleagues in adult surgery^[37]. Reports suggest anywhere between 25 and 50 cases are required to learn a single new laparoscopic procedure^[38]. We believe that robotic surgery has a clear advantage over thoracoscopic surgery simply because the fulcrum effect is no longer a problem.

Robotic thoracoscopic surgery has been successfully applied to the removal of mediastinal masses or cysts, such as bronchogenic cyst, teratoma, esophageal duplication, esophageal leiomyoma, neurogenic tumor, and thymic pathology^[39].

Radical thymectomy is the comprehensive treatment of myasthenia gravis. The feasibility and effectiveness of robotic thymectomy is evident in this cohort study^[40].

In addition, performing the “early thymectomy” (performed within a year of diagnosis) resulted in higher remission rates compared to “late thymectomy”^[41], including minimizing the adverse effects of immunosuppression in pediatric patients^[42].

Other intra-thoracic pathologies that have been treated with RATS are tracheomalacia and resection of a right paraspinal mass^[43,44].

Congenital diaphragm abnormalities, including eventration and Morgagni and Bochdalek diaphragmatic hernias, have been successfully repaired through the use of conventional MIS. However, some reports have shown a high recurrence rate for some defects, potentially due to the difficulty associated with rigid instruments. Robotic surgery is the alternative to close diaphragmatic hernias more efficiently^[45].

Acquired anomalies, such as diaphragmatic paralysis, can also be resolved with RATS. The experience of other authors and ours confirms that robotic surgery is safe and effective for repairing diaphragm abnormalities in children^[23,45]. Slater and Meehan^[45] preferred the thoracic approach for repairing Bochdalek congenital diaphragmatic hernia, but sometimes smaller babies, less than 2.5 kg, can improve

with the abdominal approach, since articulated instruments require considerable length to maneuver. The authors operated by abdominal approach on a case of Morgagni congenital diaphragmatic hernia and another case of Bochdalek congenital diaphragmatic hernia.

Regardless of the fact that thoracoscopic surgery in newborns is demanding for the surgeon and the patient, surgeons with large experience in MIS, with advanced skills, and with learning curve overcome, can perform complex procedures with efficacy and safety, such as thoracoscopic repair of esophageal atresia with tracheoesophageal fistula^[46], and even repair of long-gap esophageal atresia^[47].

In our series of 11 RATS cases, five patients weighed between 5.93 and 10.6 kg, three had diaphragmatic plication, and two lobectomy. The case of conversion to thoracotomy was a 7.8 kg patient with pulmonary sequestration, being our first robotic lobectomy. The reason for the conversion was the difficulty in maneuvering the articulated instruments. Then, in the second lobectomy, the smallest patient in our series of cases (5.93 kg), we made a totally cephalic (longitudinal) docking and placed the trocars only penetrating the thickness of the thoracic wall, with which we obtained a better space inside the thoracic cavity and we could perform a comfortable and safe lobectomy [Figure 1]. The three cases of diaphragmatic plication were performed without problems with RATS.

The application of MIS for the treatment of malignant solid tumors in children is very controversial. From 1966 to February 2011, the authors were unable to identify randomized controlled trials or controlled clinical trials that evaluated MIS in the treatment of intra-thoracic or intra-abdominal solid neoplasms in children; therefore, no definitive conclusions could be drawn about the results of MIS in these patients. Based on the available evidence at that time, the authors could not give recommendations for the use of MIS in the treatment of solid malignancies in children^[48].

Following the publication of the above conclusions, several case series of intra-thoracic solid tumors treated with VATS in children have been published.

The efficacy and safety of resection of mediastinal tumors in children were compared, using thoracotomy in 10 cases and VATS in 21 cases. The approach was indicated as non-randomized, and the analysis of the results was retrospective. The VATS group required significantly fewer blood transfusions, shorter duration of thoracic drainage, and shorter hospital stay, thus suggesting VATS is less invasive^[49].

Another series was of 17 children with thoracic neurogenic tumors, with an average weight of 11.9 kg (range: 9.3-27.4 kg). The series consisted of ten children with neuroblastoma, four with ganglioneuroma, and three with ganglioneuroblastoma. Complete thoracoscopic resection was performed in all cases. There were no deaths and no recurrence was observed during the follow-up period of 8.9-28.6 months. VATS resection of mediastinal neurogenic tumors in children offers good results. The main advantages of this approach are it avoids thoracotomy complications and improves surgical accuracy by having a better view of the anatomy^[50].

Irtan *et al.*^[51] published a series of 39 patients undergoing MIS due to neuroblastic tumors, using thoracoscopy in 20 patients, retroperitoneoscopy in 1 patient, and laparoscopy in 18 patients. The average diameter was 35 mm for thoracic tumors (range 7-85 mm). Resection was incomplete in six thoracic tumors and one adrenal tumor. Conversion was necessary in three cases of thoracic tumors. PO complications occurred in five patients. The overall survival rate was 98%. The authors concluded that, in carefully selected cases, MIS allows the safe and efficient resection of neuroblastic tumors in children.

Publications on the treatment of malignant tumors in children by RATS are only from isolated cases. Meehan and Sandler^[36] reported a case of mediastinal germ cell tumor, a ganglioneuroma, a

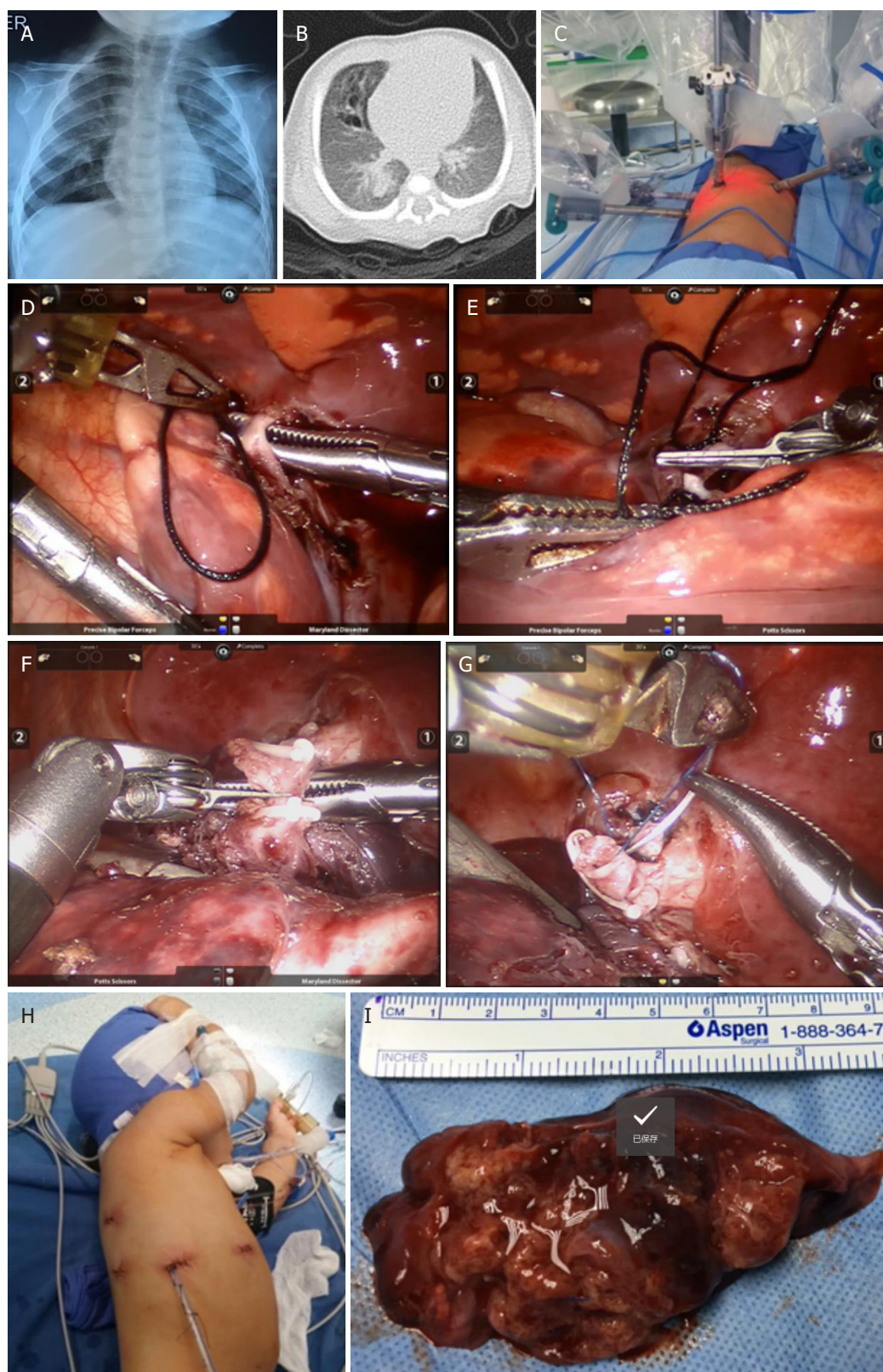


Figure 1. Robotics lobectomy technique in an infant patient. Female patient, 10 months old and 5.93 kg in weight. A, B: chest X-ray and CT scan image showing the right lower lobe affected by CCAM; C: location of the two 8-mm robot instrument trocars, an 8.5-mm trocar for camera lens, and an auxiliary 5-mm trocar in the right hemithorax and cephalic docking; D, E: IO images, dissection, ligation, and cutting of the pulmonary vein of the affected lobe; F, G: IO images, management of the lobular bronchus with hemoclip and suture; H: the complete lobectomy and pleural tube emerge through the wound to the trocar of the camera lens; I: the surgical piece was removed through the trocar wound of the camera lens. CCAM: congenital cystic adenomatoid malformation; IO: Intraoperative

ganglioneuroblastoma, a teratoma, and an inflammatory mass of unclear etiology. They concluded the robotic surgery is safe and effective for resecting solid mediastinal tumors. The application of RATS in malignant solid tumors in children in selected cases is an option, but oncological surgical principles should be applied.

Due to the low frequency of thoracic surgery in children, it was difficult to include a control or comparative group in our study, this being its main weakness.

According to the detailed non-systematic review of previous publications in PubMed on non-cardiovascular thoracic pathology treated with robotic surgery in the pediatric population worldwide, currently, the number of children treated with this technology barely has reached 100 cases, and all related references with the theme are included^[11,22,26-34,36,39,44,45].

In conclusion, This pediatric series of RATS reports a small number of patients according to the low percentage of thoracic surgery in this population. The most frequent surgical techniques performed by RATS in children are: lobectomy, resection of benign masses and mediastinal cysts, thymectomy, plication, and closure of diaphragmatic defects. RATS in newborns and infants is a very difficult technique when they weigh between 3 and 5 kg, and patients under 3 kg are not candidates for this approach at present. Based on currently available evidence, it is not possible to suggest recommendations for the use of MIS for the treatment of intra-thoracic malignant tumors in children, including the robotic surgery. Currently, few children with malignant tumors treated with RATS have been reported. Its application in selected cases is an option, but oncological surgical principles should be applied. Our results are encouraging in RATS, although our experience is limited to a few cases. Robotic surgery for the treatment of thoracic pathology is feasible and safe, and has advantages. To date, few pediatric surgeons worldwide have applied RATS in children.

DECLARATIONS

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Authors' contributions

The author contributed solely to the article.

Availability of data and materials

The author cannot share the data according to the policy of the hospital institution, for reasons of confidentiality.

Financial support and sponsorship

None.

Conflicts of interest

The author declares to be Proctor of the da Vinci Surgical System and sometimes receives salary for advice to Surgeons in their first robotic procedures, from the marketing company in my country, as part of the support in the training of surgeons by this company. However, in relation to the treatment of patients and the execution of this manuscript, no economic financing was received from commercial companies.

Ethical approval and consent to participate

In relation to ethical considerations of the study, being of an observational nature, it was not necessary to obtain the informed consent for the patients to enter the study. The Research Ethics Committee of the Hospital evaluated and approved the study. In order to perform the medical-surgical procedures, we obtained the informed consent in writing from the parents or guardians.

Consent for publication

Not applicable.

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Technical Note

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Subxiphoid uniportal video assisted thoracoscopic lobectomy in a pediatric patient

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Abstract

Thoracoscopic surgeries have witnessed tremendous and prompt recent development, especially in the field of uniportal video assisted thoracoscopic surgery (VATS) surgery. It is now possible to perform the most complex surgeries through this technique, which is of great benefit to the patient by significantly reducing the level of postoperative pain and complications of surgery. As surgeons gain experience in this field, their confidence and ability to push the limits and develop technologies are increasing. Performing uniportal VATS surgeries in children is a significant challenge for the surgeon due to the limited size of the thoracic cavity and the difficulty of the instrumentation. Here, we report the first case in the literature (as far as we know) of a uniportal Subxiphoid VATS lobectomy in a 2.5-year-old child. In conclusion, Subxiphoid uniportal VATS lobectomy is feasible in pediatric patients and may have some benefits over the intercostal approach.

Keywords: Subxiphoid uniportal video assisted thoracoscopic surgery in pediatrics, minimally invasive thoracic surgery in children, VATS lobectomy in pediatrics, pediatric thoracic surgery

INTRODUCTION

Despite the significant development of adult thoracoscopic surgery in the last two decades, especially the uniportal video assisted thoracoscopic surgery (VATS) technique, which may be performed through the intercostal, subxiphoid, or subcostal approach, the utilization of the uniportal technique in children is still



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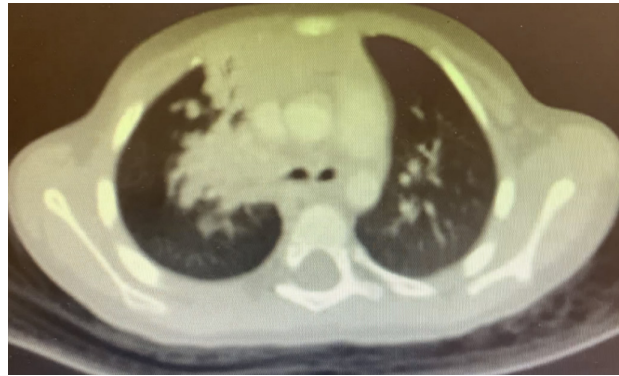


Figure 1. CT scan showing diffuse consolidation and bronchiectasis of the right upper lobe due to severe bronchomalacia



Figure 2. Left decubitus position with the right hand fixed to the right ear to open the axillary space

in its beginning and is rarely performed. The surgical literature contains very few cases, which have been conducted only by experts in this field, and most centers in the world still adopt the traditional methods, either open thoracotomy or the multiportal VATS technique^[1,2]. After gaining extensive experience in single-port surgery in all its forms in adults and performing it at an advanced level, we started to apply this technique in children as well^[3-7]. One of the challenges a surgeon may face during a lobectomy in children through the intercostal approach is the small space between the ribs, which may make the instrumentation very difficult and challenging^[7]. Therefore, we found that it makes sense to perform this type of operation via the subxiphoid approach, which may provide more space for the instrumentation in addition to comfortable angles for the instruments during the dissection of the hilum. In this article, we report the first case of subxiphoid uniportal VATS lobectomy conducted for a 2.5-year-old child, and we review some of the observations we found during the surgery.

CASE PRESENTATION

A thirty-month-old male patient suffered from recurrent chest infections since birth, which necessitated several hospital admissions and antibiotics therapy. The chest CT scan showed right upper lobe consolidation and bronchiectasis [Figure 1]. Bronchoscopy was performed to rule out any intrinsic factor or other associated anomalies. The procedure showed a significant narrowing of the right upper lobe bronchus due to severe bronchomalacia. The echocardiogram showed no cardiac abnormalities. The multidisciplinary team forum decided that lobectomy is indicated.

Surgical technique

The operation was performed under general anesthesia. Isolated right lung ventilation was obtained by advancing an uncuffed single-lumen endotracheal tube to the left main bronchus. The baby was positioned



Figure 3. An image showing the chest drainage through the same incision after its closure

in the left decubitus position with two overlapped towel sheets supporting both sides. The right hand was fixed to the right ear to open the axillary space [Figure 2]. A 3-cm incision was made over the xiphoid process [Figure 3]. The subcutaneous tissue was dissected and the insertions of the rectus muscles to both costal arches were divided at the midline. The cartilaginous xiphoid process was excised using surgical scissors. The left pleural space was opened by blunt finger dissection. A wound protector was placed, through which a 30°/5-mm video thoracoscope and all thoracoscopic instruments were introduced into the right pleural cavity.

The right upper lobe was grasped using a lung grasper and then retracted posteriorly and caudally to expose the hilar structures. Specially designed curved tip spatula, harmonic energy device, and fine vascular clamp dissector were used to dissect and encircle the right superior pulmonary vein. Advancing a stapler to divide the vein through the same incision was smooth and more natural than the intercostal approach, and the angles for the staplers were more convenient. The right superior pulmonary vein was stapled using a vascular stapler (Endo GIA™ Curved Tip Reload with Tri-Staple™ Technology) [Video 1]. The pulmonary artery was subsequently approached; dissecting and encircling the truncus anterior branch of the pulmonary artery was performed; and the branches were divided after applying two metal clips (5-mm Endo Clip™) using a harmonic scalpel [Video 1]. The left upper lobe bronchus was identified, dissected, and encircled; the vascular stapler (Endo GIA™ Curved Tip Reload with Tri-Staple™ Technology) was advanced; and the bronchus was divided. The fissure was completed and divided, including the posterior ascending arterial branch, using a vascular stapler (Endo GIA™ Reload with Tri-Staple™ Technology). The resected lobe was extracted out of the thoracic cavity, and the endotracheal tube was withdrawn a few centimeters to check the patency of the lower lobe bronchus with inflation test. Hemostasis was done, a 14-fr chest drain was inserted through the same incision, and an 8-fr intercostal microtube was introduced into the pleural space [Figure 3]. The incision was closed in layers, and the patient was extubated and transferred to the pediatrics intensive care unit in a stable condition.

Postoperative course

The baby was transferred to the pediatric ward 24 h after the surgery. There were no complications, and the chest drains were removed on the third postoperative day (POD). The patient was discharged from the hospital on the sixth POD in excellent condition [Figure 4].

DISCUSSION

Since Rodgers and Talbert^[8] introduced the thoracoscopic surgery in pediatrics in the 1970s, the topic has not attracted much attention in the field due to some difficulties. Rothenberg is one of the pioneers



Figure 4. The subxiphoid wound, one week after surgery

who developed the multiportal VATS technique for pediatrics over the last three decades^[1,2,9]. Besides the cosmetic and early postoperative morbidity concerns, some of the crucial benefits of thoracoscopic surgery in children (which may not affect the adult patients) are decreasing the risk of musculoskeletal deformity (asymmetric chest wall, scoliosis, rib fusion, and winged scapula) that may be noted after posterolateral thoracotomy in younger patients^[10-12]. In adult patients, a natural progression and evolving of thoracoscopic techniques resulted recently in the evolution of uniportal VATS technique^[3-6,13]. Mastering the technique of uniportal VATS in adults requires intensive training to pass the learning curve to be applied safely in adults^[6]. The subxiphoid approach is a new addition to the uniportal VATS technique. The subxiphoid area is distinguished from the intercostal by being nerveless, which allows avoiding injury to the intercostal nerve during operation^[14,15]. Besides, the proper angles for the instruments and staplers, which intersect at a 90° angle with the hilar structures, are more streamlined and comfortable to the operator. However, the subxiphoid approach is not devoid of challenges; the need to compress the pericardium occasionally during surgery and the distance of the work area from the incision requires specialized training and experience. In children, this technique may require additional skills. It could be more challenging to the surgeon for many reasons, including the difficulty of obtaining isolated lung ventilation due to the lack of a double-lumen endotracheal tube in young children, in addition to the lack of appropriate instruments with the curved tip specially designed for uniportal VATS operations. A few reports and studies have recently been published on the utilization of uniportal VATS for anatomical resections in pediatrics^[7,16-18]. However, the literature does not yet contain a report on subxiphoid uniportal VATS anatomical resection in a pediatric patient. To our knowledge, this is the first case in which an anatomical resection was performed for a patient of this age and weight via subxiphoid uniportal VATS approach.

In conclusion, in expert hands, subxiphoid uniportal VATS lobectomy in pediatrics may be safe and may have benefits to the patient. The surgeon's experience in this type of surgery in adults is crucial before starting to apply it to pediatrics. There is a need to design suitable instruments and staplers for this type of surgery in pediatrics. There is, of course, also a need to run a comparative study with an appropriate cohort of patients before determining the safety and feasibility of this technique in pediatrics.

DECLARATIONS

Authors' contributions

Conception and design of the study and performed data analysis and interpretation: Abu Akar F, Shaqqura B
 Performed data acquisition, as well provided administrative, technical, and material support: Abu Akar F, Jiang L, Rumman N

Availability of data and materials

The authors declares that all the data that support our findings can be found in our database and archive at Al-Makassed Hospital. Data can be deposited into data repositories or published as supplementary information in the journal.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval and consent has been obtained from the patient's parents to publish the article.

Consent for publication

Not applicable.

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Review

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Robotic lobectomy costs and quality of life

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Abstract

The surgical approach for lobectomy has changed over time with recent data demonstrating that the majority are performed using a minimally invasive approach. While the use of the robotic platform for pulmonary resection has been shown to have acceptable clinical outcomes, cost and quality of life need to be considered when starting a robotic lobectomy program. In this review, we evaluate the literature on cost of robotic lobectomy and quality of life. The results suggest that early experience in a robotic lobectomy program may be associated with relatively higher index hospital costs when compared to video-assisted thoracoscopic surgery; however, with increased experience and volume, the difference may no longer be of significance. When compared with thoracotomy, the cost is comparable if not less costly and may even be profitable for the hospital. Quality of life appears to be acceptable in the early experience of robotic lobectomy.

Keywords: Robotic, thoracic surgery, lobectomy, cost, quality of life, patient reported outcomes

INTRODUCTION

The surgical approach for pulmonary lobectomy has significantly changed over time. Two decades ago, the majority of lobectomies were performed via thoracotomy. Over time, surgeons began to adopt video-assisted thoracoscopic surgery (VATS) and an increased proportion of lobectomies were performed using this minimally invasive approach. The da Vinci Surgical System (Intuitive Surgical; Sunnyvale, California, USA) later provided an alternative platform. The proportion of lobectomies after introduction



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of this system performed by thoracotomy continued to decline. One study showed that, in 2008, 76.2% of lobectomies were performed using the open approach, compared with 23.4% and < 1.0% for VATS and robotic approaches, respectively^[1]. In 2014, the majority of lobectomies was no longer performed via the open approach, and VATS and robotic approaches comprised 31.6% and 25.0% of lobectomies, respectively^[1]. Another study demonstrated that, from 2011 to 2015, lobectomies performed by thoracotomy had an absolute decline of 11.5%^[2]. Lobectomies performed using the robotic approach had an absolute increase of 10%, yet VATS only had an absolute increase of 1.5%^[2].

While the use of the robotic platform for lobectomy is growing and its safety has been evaluated and found to be acceptable^[2-5], additional considerations for utilizing the robotic approach over other techniques and starting a robotic lobectomy program are still under evaluation, including costs and patient reported outcomes (PRO). A systematic review of the literature on the cost of robotic-assisted lobectomy that was performed by Singer *et al.*^[6] from our institution, which included six observational studies published before 1 December 2017, found that, in general, the costs of robotic lobectomy exceed those of VATS. The studies that they reviewed were primarily based on early experiences, with the study period ranging from 2007 to 2013, and were only from the USA.

In this article, an updated review of the literature of the cost of robotic lobectomy is presented and the quality of life in these patients is reviewed.

METHODS

Literature search

An electronic literature search on PubMed was performed to identify studies that included either robotic lobectomy costs or quality of life on 9 September 2019. Search terms used included: (“cost” or “charges” or “quality of life” or “patient reported outcomes”) AND (“robotic” or “robot”) AND (“lobectomy” or “anatomic resection”). Abstracts from the search result were screened for relevance to include studies that evaluated costs and/or quality of life in patients undergoing robotic lobectomy. Original articles written in English were selected. Case reports and abstract-only publications were excluded. The full-text of the remaining studies were reviewed for eligibility. Additional studies were identified from reviewing the references of the studies found in the electronic literature search.

RESULTS

The literature search for costs associated with robotic lobectomy and review of its references resulted in 16 relevant articles [Table 1] from five different countries (Canada, 1; China, 2; France, 1; Italy, 1; and USA, 11)^[1,7-21]. These articles were published from 2008 to 2019 with the study period ranging from 2008 to 2017. The number of patients undergoing robotic lobectomy ranged from 12 to 2498. All studies were observational. The majority of studies were retrospective analyses of prospectively collected data from a single institution. Other studies included one prospective observational study^[7] and four population-based cohort studies^[1,8-10]. In addition to analyzing costs of patients undergoing robotic lobectomy, seven of these studies also included patients who underwent robotic segmentectomy or wedge resection^[7,9,11,13-15,18]. The majority of studies reported using the da Vinci Si system. Only two studies noted the use of the Xi^[16,17]. Both four-arm^[11,13,14,17,18,20] and three-arm^[7,12,15,19,21] techniques were reported. There were three relevant articles identified that studied quality of life in patients undergoing robotic lobectomy^[21-23].

ROBOTIC LOBECTOMY COST

Cost definition and analysis

Costs reported in these studies were based on the index hospitalization. There was significant heterogeneity in the definition of cost, how it was analyzed, and the detail provided of these costs. Studies reported total

Table 1. Summary of robotic lobectomy cost studies

First author	Published	Study period	n	Type	Early experience	OR time (min)	Comparison groups	Model	Technique	Institution/Database	Country
Glenn <i>et al.</i> ^[6]	2019	2010-2013	1434	Retrospective PSM	-	-	VATS	-	-	Database (NIS)	USA
Kneuert <i>et al.</i> ^[17]	2019	Jan 2012-Sep 2017	296	Retrospective PSM-IPTW	No	287.2 (mean)	VATS open	Si Xi (2016)	4 arms	OSU (three surgeons)	USA
Li <i>et al.</i> ^[19]	2019	May 2013-Apr 2016	230	Retrospective PSM	No (first robotic assisted surgery in 2009)	90.8 (average)	VATS	S	3 arms	Shanghai Chest Hospital	China
Nelson <i>et al.</i> ^[16]	2019	2011-2017	106	Retrospective PSM-IPTW	No	226 (median)	VATS open	Si Xi	Total portal technique	MD Anderson (two surgeons)	USA
Subramanian <i>et al.</i> ^[1]	2019	2008-2014	1929	Retrospective	-	-	VATS open	-	-	Database (HCUP Florida SID)	USA
Worrell <i>et al.</i> ^[21]	2019	Nov 2010-Mar 2012	25	Retrospective	Yes (first 25 robotic lobectomies)	231	VATS	Si	3 arms	University of Michigan	USA
Kaur <i>et al.</i> ^[11]	2018	Apr 2014-Mar 2015	40 (42)*	Retrospective	Yes (first year of robotic thoracic oncology)	324 (mean) [‡]	VATS	Si	4 arms	St. Joseph's Healthcare Hamilton (two surgeons)	Canada
Novellis <i>et al.</i> ^[14]	2018	May 2015-Mar 2016	21 (23)*	Retrospective	No	150 (median) [‡]	VATS open	-	4 arms	-	Italy
Gondé <i>et al.</i> ^[7]	2017	Sep 2014-Sep 2015	39 (57)*	Prospective observational	No (robotic lobectomy since 2012)	255 (median) [‡]	VATS	Si	3 arms	Rouen University	France
Bao <i>et al.</i> ^[18]	2016	Sep 2014-Jul 2015	64 (71)*	Retrospective PSM	Yes (but excluded first 30 robotic cases)	136 (mean) [‡]	VATS	-	4 arms	First Affiliated Hospital of Zhejiang University	China
Deen <i>et al.</i> ^[15]	2014	2008-2012	50 (57)*	Retrospective	-	223 [‡]	VATS open	Si	3 arms	Swedish	USA
Nasir <i>et al.</i> ^[13]	2014	Feb 2010-Oct 2013	282 (394)**	Retrospective	No	107 (median) [‡]	None	Si	4 arms	UAB (single surgeon)	USA
Paul <i>et al.</i> ^[10]	2014	2008-2011	2498	Retrospective	-	-	VATS	-	-	Database (NIS)	USA
Spillane <i>et al.</i> ^[20]	2014	Jun 2011-Dec 2012	22	Retrospective case-control	Yes (first year)	261	VATS	Si	4 arms	Cape Cod Hospital (single surgeon)	USA
Swanson <i>et al.</i> ^[9]	2014	2009-2011	295 (620)*	Retrospective PSM	-	255 (median)	VATS	-	-	Database (premier)	USA
Parke <i>et al.</i> ^[4]	2008	2007	12	Retrospective	-	217	VATS open	Si	3 arms	MSKCC	USA

[‡]Value includes robotic surgical resection other than lobectomy. *Number includes robotic lobectomy, segmentectomy, and/or non-anatomic resections. **Number includes robotic lobectomy, segmentectomy, and conversions to open. OR: operating room; n: number of robotic lobectomies performed; VATS: video-assisted thoracoscopic surgery; USA: United States of America; OSU: Ohio State University; UAB: University of Alabama; NIS: national inpatient sample; MSKCC: Memorial Sloan Kettering Cancer Center; HCUP: Healthcare Cost and Utilization Project; SID: State Inpatient Database; PSM: propensity score matching; IPTW: inverse probability of treatment weighting

costs, direct costs, and/or indirect costs. Details on operating room (OR) charges and costs were provided by some studies. Professional fees were included in some studies, but not all. The micro-costing method was used to assess costs in the studies by Kaur *et al.*^[11] and Gondé *et al.*^[7] Relative cost, rather than absolute cost, was reported in the study by Park^[12].

Total costs were reported as the sum of indirect and direct costs in the study by Nasir *et al.*^[13]. Direct cost was defined as the cost of any items used and services provided in the care of the patient during the hospitalization. This included all operating room disposable equipment and supplies; staplers; laboratory tests; imaging studies; pharmacy items and medications; and salaries and benefits of personnel who delivered care to the patient. Indirect cost was defined as overhead cost and amortization of capital equipment and supplies and maintenance.

Robotic specific costs were defined and reported by many studies and included direct costs such as disposable instruments, drapes, and other supplies. Other robotic specific costs provided included amortized cost/capital depreciation and maintenance costs. Robot depreciation in the study by Novellis *et al.*^[14] was estimated from capital cost of 2 million euros plus annual maintenance of 200,000 euros divided by the number of procedures per year (400 cases) over eight years. Deen *et al.*^[15] calculated capital depreciation and service cost of 1200 USA dollars (USD) per case by considering four robots priced at two million USD each, performing 2403 procedures in a 22-month period. Gondé *et al.*^[7] calculated capital depreciation by dividing the sum of the purchase price and maintenance cost by the number of surgical procedures per year multiplied by the depreciation period. In the study by Nelson *et al.*^[16], the depreciation was calculated over five years. Some studies included these costs in the total hospitalization cost, while others did not. In the study by Kaur *et al.*^[11], these costs were excluded since they were reported to be covered by philanthropic subsidies and assumed no extra cost to the public health system of Canada. In the population-based study by Swanson *et al.*^[9], the cost that they reported incorporated the cost of the procedure to the hospital, but not the acquisition and annual maintenance cost of the robot.

In the prospective study by Gondé *et al.*^[7], total cost was defined by length of stay related costs (clinical expense, medical logistics, general logistics, and buildings) and costs independent of length of stay (direct charges including medical supplies and medico-technical expenses including capital depreciation). Part of the cost calculations in this study was based on the French National Cost Study database. In two population-based studies, Subramanian *et al.*^[1] and Paul *et al.*^[10] estimated costs by using total hospitalization charges and applying hospital-specific cost-to-charge ratios. It is unclear how cost was derived in the study by Glenn *et al.*^[8], another population-based study, which had the highest total cost (102,057 USD) reported of all studies. In the study by Novellis *et al.*^[14], estimated cost was reported as percentage of regional health service reimbursement. This was derived from using actual costs as well as estimated costs.

Cost comparison of robotic lobectomy to vats and open lobectomy

Six of 16 studies compared the cost of robotic lobectomy to both VATS and open approaches [Table 2]^[1,12,14-17]. Two studies found no significant difference in adjusted costs when comparing robotic approach to either VATS or open approach for the total hospital stay^[16,17]; however, one of these studies noted that it may have been underpowered to detect a difference between groups^[16]. Both studies used propensity score adjustment by inverse probability of treatment weighting. The study by Kneuert *et al.*^[17] did not find a difference in OR costs when comparing robotic to VATS (USD 9912 vs. USD 9491; $P = 0.44$); however, open approach had lower operating room costs than robotic (USD 8698 vs. USD 9912; $P < 0.01$). They observed an inverse relationship between OR related costs and postoperative related costs. Deen *et al.*^[15] found that the overall cost for robotic approach was significantly higher than VATS (\$17,011 vs. \$13,829; $P < 0.001$), but did not find a significant difference when compared to open approach (\$17,011 vs. \$15,036; $P = 0.058$).

Table 2. Comparison by surgical approach (robotic, VATS, and open)

First author/year published	n		OR time (min)			LOS (days)			Cost			Robotic vs. Robotic vs.			
	Robot	VATS	Open	Robot	VATS	Open	Robot	VATS	Open	Description	Robotic	VATS	Open	VATS	open
Kneuerztz <i>et al.</i> ^[17] 2019	296	161	240	278	289*	265*	3.8	3.8	5.4*	Total direct costs, IPTW-adjusted (USD) Total indirect costs, IPTW-adjusted OR costs (2012-2015) Total charges	\$17,223 \$17,215 \$9912 \$119,180	\$17,260 \$16,415 \$9491 \$124,026	\$18,075 \$16,993 \$8698 \$120,811	<i>P</i> > 0.99 <i>P</i> = 0.55 <i>P</i> = 0.44 <i>P</i> = 0.61	<i>P</i> = 0.48 <i>P</i> = 0.94 <i>P</i> < 0.01 <i>P</i> = 0.93
Nelson <i>et al.</i> ^[16] 2019	106	301	424	226	173*	148*	4	4	5*	Unadjusted costs, robotic vs. VATS: 23.3% higher Adjusted costs, robotic vs. VATS Unadjusted costs, robotic vs. open: 10.1% higher Adjusted cost, robotic vs. open	- - - - -	- - - - -	- - - - -	<i>P</i> = 0.003 <i>P</i> = 0.368 <i>P</i> = 0.159 <i>P</i> = 0.184	- - - -
Subramanian <i>et al.</i> ^[1] 2019	1929	4608	8501	-	-	-	4	5*	7*	Index hospital cost (USD)	\$20,377	\$17,802	\$17,200	<i>P</i> < 0.001	<i>P</i> < 0.001
Novellis <i>et al.</i> ^[14] 2018 [‡]	21	42	38	150	189*	112*	4	5*	6*	Total direct costs, mean (Euros) Operating room costs, mean Hospital stay, mean Robotic consumables Depreciation	€6799 €1349 €920 €2062 €532	€5132 €1443 €1427 - -	€5244 €1094 €1944 - -	- - - -	-
Deen <i>et al.</i> ^[15] 2014	57	58	69	223	202*	180*	4.62	4.75	5.47	Overall cost (USD) Operating room costs	\$17,011 \$5243	\$13,829 \$4520	\$15,036 \$4301	<i>P</i> < 0.001 <i>P</i> < 0.001	<i>P</i> = 0.058 <i>P</i> < 0.001
Park <i>et al.</i> ^[43] 2008	12	87	269	217	225	223	4	4	6	Total "relative" average costs (USD)	\$4380	\$399	\$8368	-	-

[‡]Study included two robotic segmentectomies and one open segmentectomy, not included in the *n* value. *When compared with robotic approach, the difference is statistically significant. VATS: video-assisted thoracoscopic surgery; LOS: length of stay; OR: operating room; USD: US dollar; IPTW: inverse probability of treatment weighting; *n*: number of robotic lobectomies

OR costs and time were both higher in the robotic group when compared to either VATS or open group, but there was no significant difference for length of stay. A population-based study by Subramanian *et al.* [1] found a significantly higher index hospital cost for robotic lobectomy when compared with VATS and open approaches (robotic \$20,377, VATS \$17,802, and open \$17,200; $P < 0.001$). The study by Park [12] found that robotic-assisted lobectomy was less expensive than open approach.

Nine studies compared the cost of robotic lobectomy with VATS only [Table 3] [7-11,18,20,21]. All of these studies found a significantly higher total cost in the robotic group when compared to VATS. When provided, the intraoperative costs or charges were also significantly higher in the robotic group.

Profit

Two studies discussed costs in terms of profit, one from the USA and the other from Italy [13,14]. Nasir *et al.* [13] evaluated patients undergoing robotic lobectomies and segmentectomies during 2010-2013 at a single institution in the US, performed by a single surgeon using only Medicare patients. The median

Table 3. Comparison by surgical approach (robotic and VATS)

First author/year published	n		OR time (min)		LOS (days)		Costs		Robotic vs. VATS
	Robotic	VATS	Robotic	VATS	Robotic	VATS	Robotic	VATS	
Glenn <i>et al.</i> [68] 2019	1434	1434	-	-	6.09	6.597	Total cost (USD)	\$102,057	$P < 0.001$
Li <i>et al.</i> [99] 2019	230	230	90.84	92.25	4.97*	5.45*	Total hospital cost (CNY)	93,245	$P = 0.000$
Worrell <i>et al.</i> [20] 2019	25	73	231*	183*	3	4	Total direct fixed + variable cost (USD)	\$13,122	$P < 0.05$
							OR costs, direct fixed + variable	\$7575	$P < 0.0001$
							OR supply cost	\$5757	$P < 0.0001$
Kaur <i>et al.</i> [10] 2018	40 (42)**	68 (96)**	324**	211**	5.09‡	5.03‡	Hospital costs, median (USD)‡	\$15,247	$P < 0.001$
							Intraoperative cost, median‡	\$9377	$P = 0.000$
Gondé <i>et al.</i> [7] 2017	39 (57)**	49 (55)**	255	255	5‡	6‡	Total costs, median (Euros)‡	€10,972	$P = 0.007$
							Supplies, median‡	€3236	$P = 0.004$
							Stapler, median‡	€1670	$P = 0.036$
Bao <i>et al.</i> [108] 2016	62 (69)**	62 (69)**	136**	111**	7.6‡	6.4‡	Hospital cost, mean (USD)‡	\$12,067	$P < 0.001$
Paul <i>et al.</i> [100] 2014	2498	37,595	-	-	5	5	Estimated total costs, median (USD)	\$22,582	$P < 0.001$
							Total charges, median	\$79,375	$P < 0.001$
Swanson <i>et al.</i> [9] 2014	295	295	4.49	4.23	6.07	5.83	Total hospital cost, mean (USD)	\$25,041	$P = 0.0001$
							Total hospital cost, median	\$21,833	
Spillane <i>et al.</i> [200] 2014	22	22	261*	159*	4.36*	5.45*	Mean total hospital charges (USD)	\$34,635	$P = 0.0125$
							Operation room charges	\$11,862	$P < 0.0001$

*Statistically significant difference. **Number includes lobectomies and segmentectomies. ‡Value includes surgical resection other than lobectomy. VATS: video-assisted thoracoscopic surgery; n: number of lobectomies; USD: US dollars; CNY: Chinese Yuan; OR: operating room; LOS: length of stay

profit margin per patient was \$3497. This was based on a median Medicare reimbursement of \$18,937 and total median expense of \$15,440 per patient. Profit margin was defined by the amount of reimbursement subtracted by the total expenses (direct and indirect costs) of the patient encounter.

In the study by Novellis *et al.* [14], robotic lobectomy and segmentectomy performed for early stage lung cancer had higher costs when compared with VATS and open approaches; however, the estimated cost was 82% of the regional health service reimbursement for robotic approach, still resulting in a profit for the institution. The other two approaches were also profitable with estimated costs of 68% and 69% of reimbursement for VATS and open approaches, respectively.

QUALITY OF LIFE

Lacroix *et al.* [22] presented a single-center, retrospective analysis of 61 consecutive patients who underwent robotic lobectomy during its introduction to their unit from December 2012 to August 2015. They defined the learning period as their first 22 lobectomies and assessed quality of life (QOL) using the 36-Item Short Form Survey (SF-36) at midterm follow-up for the remaining 39 patients in their study. The mean physical component scale (PCS) score was 64.3 ± 17.6 and the mean mental component scale (MCS) score was 62.6 ± 19.6 . The SF-36 was previously used at their institution to assess QOL for chest wall resection

surgery, resulting in a mean PCS score of 40 and MCS score of 44. They found an association between pain and PCS scores, where PCS scores were significantly lower in patients with moderate pain (51.6 ± 14.2) than those with mild (69.4 ± 17.7) or no pain (67.8 ± 16.1) ($P = 0.05$). They concluded that QOL was satisfactory in their early experience for robotic lobectomy and was related to the pain level.

In the study by Worrell *et al.*^[21], costs and quality of life outcomes were evaluated during the initiation of their robotic lobectomy program. They compared their first 25 robotic assisted lobectomies with 73 VATS lobectomies, which were performed from 2010 to 2012. The European Organization for Research and Treatment of Cancer quality of life questionnaire (QLQ-30) was used to assess QOL with responses from 29 of the 98 patients, 9 robotic and 20 VATS, at a median follow-up of 65 months. This study found no significant difference between the robotic and VATS groups in their global health status and symptom scale median scores.

In a retrospective study, Cerfolio *et al.*^[23] reported a consecutive series of patients with clinically apparent resectable non-small cell lung cancer (NSCLC) from February 2010 to April 2011 who underwent attempted completely portal robot lobectomy using the four-arm technique. This group was compared against propensity-matched controls who underwent nerve- and rib-sparing thoracotomy. The study was performed by a single surgeon at a single institution. Quality of life information was obtained at two time points, three weeks and four months after surgery, and was measured by the Short Form Health Survey (SF-12) with supplemental questions about pain control. The robotic lobectomy group had a significantly higher average mental quality of life (MCS) score at three weeks when compared with the thoracotomy controls (53.5 vs. 40.3; $P < 0.001$). A trend for higher physical quality of life (PCS) score at three weeks was observed with the robotic group, although it was not of statistical significance (40.3 vs. 43.1; $P = 0.07$). There was no significant difference observed for mental or physical quality of life at four months. The authors in this study noted that there may have been bias introduced in the surveys since the patients were informed that the robotic approach was a new and “less invasive” technique.

DISCUSSION

The hospital cost of robotic lobectomy during initiation of a robotic lobectomy program and/or early experiences at an institution has consistently been shown to be higher when compared to VATS lobectomy^[11,18,20,21]. There were many factors observed to affect total hospital cost, one of which was intraoperative cost. Studies that disclosed OR time during early experiences reported a significantly longer time for robotic lobectomies when compared to VATS [Table 3]^[11,18,20,21]. Two of these studies observed a decrease in operating time with more experience, which translated into a difference in intraoperative cost^[11,20]. Kaur *et al.*^[11] found that, based on their micro-costing analysis, anatomic resections using the robotic approach cost more than VATS by \$3116 per case. They considered significantly higher intraoperative times to be a main contributor to this difference, and reported that OR time using the robotic platform decreased over time. There was a mean difference of 71 min ($P = 0.004$) when comparing the first 20 robotic resections with the remaining 22 robotic resections, which resulted in an intraoperative cost difference of \$883.38, reducing the total hospital cost. In their study, Spillane *et al.*^[20] attributed higher associated hospital charges for robotic-assisted lobectomies to increased cost of OR time. They also found a trend in a decrease in intraoperative duration with the robotic approach over time. In their study, Bao *et al.*^[18] noted that longer operative time for the robotic group may be due to the limited robotic experience of the surgeon.

This review also includes studies performed at centers with established robotic programs with high robotic surgical case volume. Case volume and surgeon experience may influence hospital costs. The amortized cost of robotic equipment is directly dependent on the number of cases performed, with higher volume

resulting in lower costs. The two studies that unexpectedly demonstrated no significant difference in adjusted cost of robotic lobectomy compared to VATS were performed at high-volume surgical centers experienced in robotic surgery. These studies also found no significant difference in cost when comparing robotic to open lobectomy. Both Si and Xi systems were used and both reported on a more recent study period with patients evaluated into the year 2017.

There are also non-operating room costs to take into consideration. Postoperative complications have been shown to increase costs^[16,24]. In Nelson's^[16] study, they reported an association between pulmonary and cardiovascular complications with increase in mean costs for all approaches. While the majority of studies in this review did not find a significant difference in overall postoperative major or minor complications between robotic and VATS or open groups^[7,8,11,14-19,21], this is a potential area for cost reduction. Kneuert *et al.*^[24] performed a retrospective review of patients at our institution who underwent robotic-assisted lobectomy for NSCLC and evaluated postoperative outcomes on cost. Postoperative complications and prolonged hospital stay added considerable hospital expenses, which was the largest variability in total cost in the study.

The studies in this review that reported a difference in postoperative complications between groups were multi-institutional database studies^[1,9]. Swanson *et al.*^[9] reported that patients undergoing lobectomy via robotic approach from 2009 to 2011 were 4.24 times more likely to have a minor event than those undergoing VATS. In contrast, the study by Subramanian *et al.*^[1] found that, from 2009 to 2014, robotic lobectomy compared with VATS was associated with decreased adjusted risk of any minor postoperative complication, and, when compared with the open approach, had a decreased risk of any major or minor postoperative complication. Glenn *et al.*^[8] found no significant difference in overall morbidity between the robotic group and VATS group from 2010 to 2013; however, they observed that, in the earlier period of the study (2010-2011), morbidity was significantly higher in the robotic group when compared with VATS (robotic 42.9% vs. VATS 36.3%, $P = 0.004$). From 2012 to 2013, there was no longer a significant difference. Findings in these studies suggest, but do not confirm, that postoperative complications may be higher in earlier experiences of robotic lobectomy.

Based on the literature comparing all three approaches at single institutions, the cost of robotic lobectomy appears to be comparable if not less costly than open lobectomy and/or profitable. While OR time was significantly longer in the robotic group in these studies, length of stay was shorter or similar. The reduction in length of stay was noted by some authors to account for their findings. From the three studies that evaluated quality of life in their early experience, it appears that the robotic approach has acceptable results, although the number of studies and patients evaluated are limited^[21-23].

Many studies in our review compared robotic approach to VATS only, with results consistently demonstrating higher costs for robotic lobectomy. Interestingly, no study was identified during our literature search that compared costs for robotic approach to thoracotomy only even when the data suggest that the continued decline in thoracotomy for lobectomies appears mainly a result from increased adoption of the robotic platform not from increased use of VATS^[1,2]. While the majority of studies show that robotic lobectomy has higher hospital costs than VATS, the significance of this finding is unclear. The difference in index hospital cost is of statistical significance, but its overall impact on patient outcomes and health economics has not been elucidated and the value of using the robotic platform has not been defined. Further studies on patient outcomes such as quality of life, recovery time, and morbidity, as well as surgeon factors, are needed.

Study limitations

There are limitations of this study. Due to the heterogeneity of how costs were defined and analyzed, a quantitative analysis is not feasible in this study and direct comparisons between studies could not be

performed. There appears to be an overall underappreciation in the surgical literature of the differences among cost, charges, and recovery of services, which rendered comparison incredibly difficult. Additionally, there is little appreciation for the running costs that go into caring for these patients and are often assumed into operational overhead. This review was also based on observational studies, with all but one study utilizing retrospective analysis. In addition, the majority of studies reported using the Si, which is an older generation. Only two of 16 studies reviewed noted using the Xi, which was Food and Drug Administration approved and introduced to the USA in 2014. Another limitation is the limited number of studies regarding quality of life available for review. More studies on patient reported outcomes for those undergoing robotic lobectomies are needed to better understand its impact on quality of life. Finally, while we evaluated financial costs to the hospital and quality of life of patients undergoing robotic lobectomy, we did not comprehensively assess the value of the robotic platform. There are more important factors to consider beyond index hospitalization costs and PRO.

CONCLUSION

Developing a robotic lobectomy program may be associated with relatively higher index hospital costs when compared to VATS approach. With increased experience and volume of robotic cases, this difference may no longer be of significance, but additional defining of costs versus charges is needed as a surgical society. As an overall review, the cost of robotic lobectomy is comparable if not less costly than open lobectomy based on single institution studies and may be profitable for the hospital, if we can better understand the operational costs needed to care for these patients. Quality of life appears to be acceptable in the early experience of robotic lobectomy.

DECLARATIONS

Authors' contributions

Manuscript preparation: Nishimura JM

Editorial of manuscript: Nishimura JM, Goodwin M, Kneuert P, Moffatt-Bruce S, Merritt RE, D'Souza DM

Availability of data and materials

Not applicable.

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Conflicts of interest

Dr. Desmond D'Souza is a proctor for Intuitive Surgical Inc. Dr. Robert Merritt is a speaker for Intuitive Surgical Inc. All other authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Robotic *vs.* traditional stapler use in robotic portal anatomic lung resection

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Abstract

Aim: Currently, there is a paucity of data comparing robotic to traditional video-assisted thoracic surgery stapling devices and the effects on perioperative outcomes during robotic anatomic lung resection. We sought to investigate our institutional experience with patients undergoing robotic anatomic lung resection stratified by the type of stapler used over a contemporary period.

Methods: We performed a retrospective review of a prospectively maintained thoracic surgery database and evaluated all patients who underwent robotic anatomic lung resection between January 2015 and December 2018. Patients were grouped based on the type of stapler used during surgery and preoperative characteristics and intraoperative and postoperative outcomes were compared.

Results: In total, 634 lung resections occurred during the study period. Of those, 236 met inclusion criteria, and 49 cases (20.8%) fully utilized the robotic stapler. We found no clinically significant difference in preoperative or intraoperative characteristics between groups, except operative time was longer in the robot stapler group. This was likely related to surgeon learning curve. There were no differences between groups in postoperative outcomes or complications.

Conclusion: We found equivalent rates of complications, prolonged air leak, and chest tube duration between the two groups. Based on our data, we recommend that surgeons use the stapling device with which they are most confident.

Keywords: Robotic stapler, robotic lung resection, lung cancer, EndoWrist®



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INTRODUCTION

Robotic resection for lung cancer is becoming increasingly accepted by the thoracic surgery community. Several recent publications have demonstrated the feasibility, safety, and equivalent oncologic outcomes for robotic anatomic resections compared to traditional Video-Assisted Thoracic Surgery (VATS) and improved postoperative outcomes compared to traditional thoracotomy^[1-6]. Advantages of robotic resection over traditional VATS include improved visualization with three-dimensional viewing, articulated instruments, and increased flexibility in areas of limited operating space. Previous drawbacks to robotics have required an experienced bedside assistant for division of the hilar structures with a traditional VATS stapler, or for the operating surgeon to leave the console to return to the bedside to perform this critical portion of the operation. In 2014, the da Vinci Xi System (Intuitive Surgical, Sunnyvale CA) was introduced, with instrument updates in early 2016 which provided a 30-mm curved-tip stapler that was capable of providing the console surgeon the ability to control and fire staplers for division of vascular, bronchial, and parenchymal structures^[7,8]. This decreased some of the potential limitations for surgeons to perform minimally invasive anatomic lung resections by allowing a critical step to be placed back in the hands of the operating surgeon at the console^[9].

Currently, there is a paucity of data regarding the perioperative outcomes of robotic anatomic lung resection comparing robotic staplers to traditional VATS stapling devices. We sought to investigate our institutional experience with patients undergoing robotic anatomic lung resection stratified by the type of stapler used over a contemporary period.

METHODS

Patients

A retrospective analysis of an institutional review board approved prospective Thoracic Surgery database was performed. All consecutive patients who underwent lung resection between 1 January 2015 and 31 December 2018 were included. Patients were excluded if they underwent a non-anatomic resection (wedge), underwent planned or were converted to a thoracotomy, or had a VATS that did not include the use of the da Vinci robotic system [Figure 1]. The primary aim of this study was to investigate intraoperative and postoperative outcomes with the da Vinci EndoWrist® robotic stapler compared to the Covidien Endo GIA™ stapler (Medtronic, Fridley MN) in robotic anatomic lung resections. This study was approved by the Committee for the Protection of Human Subjects (#30040).

Data collection

Demographic data (age, sex, and race), pulmonary co-morbidities, operative data (operative time and stapler use), pathologic data (stage and lymph nodes collected), postoperative length of stay (LOS), and 30-day complications were obtained. Operative time, in minutes, was calculated from surgery start and stop times. Postoperative complications were monitored for 30 days from the index procedure date and graded I-IV as classified by Clavien-Dindo^[10,11]. The primary outcome of interest was presence of a postoperative prolonged air leak (PAL), which was defined as an air leak lasting more than five days, as defined by the Society of Thoracic Surgeons^[12].

Surgical technique

Anatomic lung resections were performed by two surgeons as previously described^[13]. Briefly, all resections utilized the da Vinci Xi system with a four-arm technique and an additional 15-mm assistant port. The camera and robotic ports are placed in the 6th-8th intercostal spaces, depending on the tumor site. The assistant port is placed as low as possible without traversing the diaphragm. When a traditional VATS stapler is used, 8-mm robotic trocars are placed and the stapler is introduced via the 15-mm assistant port. When the robotic stapler is used, one or two 12-mm trocars are placed, as described previously^[7]. There are limited requirements for the assistant to change instruments when the robotic stapler is used, but he/she

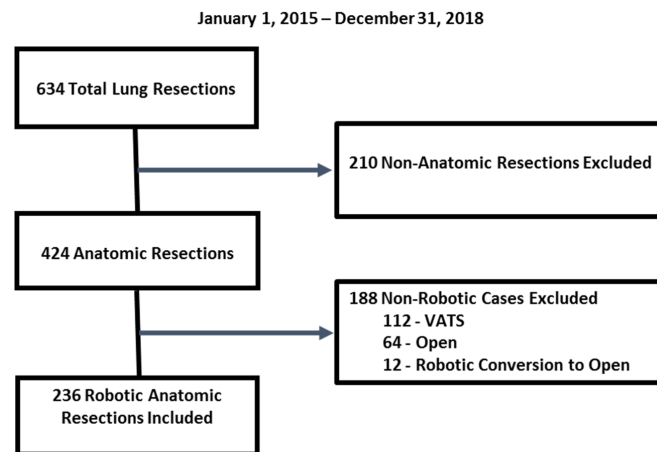


Figure 1. Study inclusion and exclusion. VATS: video-assisted thoracic surgery

maintains the ability to insert ancillary instruments and remove specimens without undocking a robotic arm. In addition, retraction and tension are controlled by the surgeon and exposure of the operative field is more stable^[14,15]. Typically, a bipolar grasper is used in the surgeon's left hand and a monopolar spatula in the right. Retraction is facilitated via a tip-up fenestrated grasper in the 3rd arm. The spatula provides excellent blunt dissection capability, has less arc than the hook, and is less sharp than the Maryland bipolar dissector. A mediastinal lymph node dissection is performed initially, as it provides exposure for portions of the bronchial and lobar lymph node dissections. The pulmonary artery in the fissure is then dissected as appropriate, limiting the dissection of lung parenchyma as much as possible. The hilar structures and lymph nodes are then circumferentially dissected. The vascular structures are often divided first, followed by the bronchus. Any remaining lung parenchyma is divided at convenient points to facilitate exposure.

Stapler

Stapler choice was at the discretion of the attending surgeon. Intuitive released the 30-mm curved EndoWrist® robotic stapler in early 2016 and the first use of this stapler at our institution occurred in September 2016. Robotic stapler use was exclusively performed by one surgeon (JDP). Typically, division of structures by staple load were: vascular (white), bronchus (green), and parenchyma (blue or green based on thickness). Hilar structures are typically divided with the 30-mm curved stapler and parenchyma with the 45-mm stapler. The Covidien Endo GIA™ 12-mm stapler with Tri-Staple™ 2.0 Intelligent Reload technology was used during the study period. Typically, division of structures by staple load were: vascular (tan), bronchus (purple), and parenchyma (tan, purple, or black based on thickness).

Analysis

Univariate analysis was performed to assess for differences in perioperative, intraoperative, and postoperative characteristics between the cases that utilized the EndroWrist® robotic stapler and those that utilized the Endo GIA™ stapler. Two-tailed student's *t*-tests were used for continuous variables and chi-square tests were used for categorical variables. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

In total, 634 lung resections occurred during the study period. Of those, 236 met inclusion criteria, and 49 cases (20.8%) utilized the robotic stapler fully. Three cases used the robotic stapler for division of the hilar structures but the Covidien stapler for division of the lung parenchyma. These three cases were classified in the Covidien stapler group. Of note, only 12 planned robotic cases were converted to open and were excluded, corresponding to a conversion rate of 4.8%. Of these 12 conversions: three were following

Table 1. Characteristics of study population

	Robotic stapler <i>n</i> = 49	Covidien stapler <i>n</i> = 187	<i>P</i>-value¹
Age, Mean (SD)	67.2 (8.3)	67.0 (9.0)	0.89
Male, (%)	25 (51.0)	77 (41.2)	0.22
Caucasian, (%)	49 (100)	184 (98.4)	x
BMI, Mean (SD)	28.4 (6.6)	27.0 (5.8)	0.14
Pack years, Mean (SD)	46.9 (24.6)	43.2 (29.2)	0.47
Smoking status ² , (%)			
Never	9 (18.4)	24 (12.8)	0.32
Former	29 (59.2)	120 (64.2)	0.52
Current	11 (22.4)	43 (23.0)	0.94
Pulmonary co-morbidities, (%)			
Asthma	7 (14.3)	11 (5.9)	0.05
COPD	14 (28.6)	49 (26.2)	0.74
Pulmonary hypertension	1 (2.0)	2 (1.1)	0.59
Emphysema	1 (2.0)	4 (2.1)	0.97
None	28 (57.1)	120 (64.2)	0.37
Pulmonary function, Mean (SD)			
FEV1 (L)	2.24 (0.6)	2.12 (0.7)	0.23
FEV1% predicted	84.2 (16.0)	80.1 (18.3)	0.15
FVC (L)	3.3 (0.9)	3.16 (0.9)	0.25
FVC% predicted	91.2 (17.9)	91.2 (17.2)	1.0
Induction therapy, (%)	5 (10.2)	18 (9.6)	0.90

¹*P*-values from student's *t*-test or chi-square test where appropriate. ²Classified at time of first consultation with a thoracic surgeon. SD: standard deviation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; x: statistics unable to be performed

induction therapy, two required a pulmonary artery plasty, and seven were related to a combination of adhesions or tumor location that limited safe dissection around critical structures. Table 1 provides a comparison of the perioperative patient characteristics between the robotic and traditional stapler groups. There was no difference in demographics between the two groups, with a mean age of 67 in both and most patients were Caucasian. The robotic stapler group had more patients with a history of asthma, (14.2% vs. 5.9%, *P* = 0.05), but otherwise did not differ in the presence of other co-morbidities. In addition, there were no differences in preoperative pulmonary function testing or rate of induction therapy.

Intraoperative characteristics between the two groups are compared in Table 2. Cases that utilized the robotic stapler had a significantly longer average operative time (224 min vs. 176 min, *P* < 0.001). Given that these cases were performed by a surgeon in the first few years of practice, this likely reflects a learning curve rather than inherent delay with use of the robotic stapler, as evidenced by a significant decrease in average operative time from 2016-2017 (*n* = 21) to 2018 (*n* = 28) (247 min vs. 207 min, respectively; *P* = 0.01). There was no difference in the average number of staple loads used per case between the two groups. While the number of staple loads may seem high, anatomic resection is often preceded by a diagnostic wedge, which obviously increases the total number of staple loads used. Pathologic staging was similar between the two groups, although there were significantly more stage IIB cases in the robotic stapler group. There were no differences in lymph node stations or total lymph nodes collected between groups.

Postoperative outcomes are compared in Table 3. There was no difference in average LOS between the two groups (median three days for both). Median chest tube duration was two days for both groups, and ~20% of patients in each group were discharged with a chest tube. The overall postoperative PAL rate was 25.8% for the entire cohort. Within the robotic stapler group, the PAL rate was 20.4%, compared to 27.3% in the Covidien stapler group (*P* = 0.33). In the robotic stapler group, one patient with a PAL underwent a bedside doxycycline pleurodesis. In the Covidien stapler group, 10 patients underwent a procedure for management (six had bedside doxycycline pleurodesis, three had endobronchial valves, and one had both bedside

Table 2. Operative characteristics of study population

	Robotic stapler <i>n</i> = 49	Covidien stapler <i>n</i> = 187	<i>P</i> -value ¹
Operative time, minutes, Mean (SD)	224 (55)	176 (48)	< 0.001
Number of staple loads ² , Mean (SD)	11.0 (3.8)	10.1 (3.6)	0.11
Resection type, (%)			
Segment	2 (4.1)	17 (9.1)	0.25
Lobe	46 (93.9)	168 (89.8)	0.39
Bi-Lobe	1 (2.0)	2 (1.1)	0.59
Tumor location, (%)			
Right upper lobectomy	18 (36.7)	62 (33.2)	0.64
Right middle lobectomy	4 (8.2)	13 (7.0)	0.77
Right lower lobectomy	8 (16.3)	33 (17.6)	0.83
Left upper lobectomy	12 (24.5)	48 (25.7)	0.87
Left lower lobectomy	6 (12.2)	29 (15.5)	0.57
Bi-lobectomy (Middle/Lower)	1 (2.0)	2 (1.1)	0.59
Pathologic stage			
IA	25 (51.0)	83 (44.4)	0.41
IB	10 (20.4)	42 (22.5)	0.76
IIA	1 (2.0)	9 (4.8)	0.39
IIB	8 (16.3)	10 (5.3)	0.01
IIIA	2 (4.1)	18 (9.6)	0.21
IIIB	1 (2.0)	1 (0.5)	0.31
IV	0	6 (3.2)	x
Other	2 (4.1)	18 (9.6)	0.21
Lymph nodes, Mean (SD)			
Total collected	14.1 (6.1)	14.7 (7.2)	0.58
N1 collected	7.7 (4.0)	7.7 (5.2)	0.98
N2 collected	6.3 (3.3)	7.0 (4.2)	0.31
Margin status, (%)			
R0	49 (100)	184 (98.4)	x
R1	0	3 (1.6)	x

¹*P*-values from student's t-test or chi-square test where appropriate. ²Excluded eight cases for insufficient staple load number data (seven Covidien and one robotic). SD: standard deviation; x: statistics unable to be performed

Table 3. Postoperative characteristics of study population

	Robot stapler <i>n</i> = 49	Covidien stapler <i>n</i> = 187	<i>P</i> -value ¹
Length of stay, days, Median (range)	3 (1-14)	3 (1-40)	0.16
Discharged with a chest tube, (%)	10 (20.4)	40 (21.4)	0.88
Chest tube duration, days, Median (range)	2 (1-23)	2 (1-43)	0.17
Grade 3/4 complication rate ² , (%)	6 (12.2)	29 (15.5)	0.57
Complications ³ , (%)			
Return to operative room ⁴	1 (2.0)	1 (0.5)	0.31
Transfusion	1 (2.0)	3 (1.6)	0.83
Prolonged air leak ⁵	10 (20.4)	51 (27.3)	0.33
Pneumonia	2 (4.1)	16 (8.6)	0.29
Pleural effusion ⁶	1 (2.0)	5 (2.7)	0.80
Atelectasis ⁷	1 (2.0)	1 (0.5)	0.31
Pneumothorax ⁸	0	10 (5.3)	x
Atrial fibrillation ⁹	0	13 (7.0)	x
Myocardial infarction	0	0	x
Readmission ³ , (%)	5 (10.2)	25 (13.4)	0.32
Pneumonia	2 (4.1)	7 (3.7)	0.91
Pneumothorax	0	5 (2.7)	x
Pleural effusion	1 (2.0)	1 (0.5)	0.31
Empyema	0	1 (0.5)	x
Infected pleural space	0	1 (0.5)	x

Atrial fibrillation	0	2 (1.1)	x
Other ¹⁰	2 (4.1)	7 (3.7)	0.91
30-day mortality, (%)	0	1 (0.5)	x

¹P-values from student's t-test or chi-square test where appropriate. ²Grade 3/4 complication as classified by Clavien-Dindo. ³Within 30-days of index procedure. ⁴Unexpected return to OR within 30-days of index procedure. ⁵Defined as an air leak that lasted beyond postoperative day 5. ⁶Requiring drainage. ⁷Requiring bronchoscopy. ⁸Requiring chest tube reinsertion. ⁹Requiring treatment. ¹⁰Includes anemia, bowel obstruction, dehydration, syncope, hyponatremia, gastrointestinal bleed, fluid overload, and thrombus. x: statistics unable to be performed

pleurodesis and endobronchial valves). There was no difference in grade ≥ 3 complications, readmissions, or 30-day mortality.

DISCUSSION

As new technology becomes available, it is important that surgeons critically evaluate its use. The 30-mm curve tip EndoWrist® stapler was introduced in March 2016. However, only a few reports to date in the literature describe its use in pulmonary resections^[7,8,16,17]. To our knowledge, the current study is the first to directly compare the robotic stapler and a traditional VATS stapler related to perioperative outcomes in robotic anatomic lung resections. We found no clinically significant differences in preoperative characteristics between the two stapler groups at our institution. There were also no clinically significant differences noted in the number of staple loads used, pathologic stage, or lymph nodes harvested. We did identify a significant increase in operative time in the group that utilized the robotic stapler. As the robotic stapler was exclusively used by a new attending surgeon, this likely represents a learning curve rather than an intrinsic delay related to stapler use, as evidenced by the significant reduction in operative time for these cases over the course of the study period. Moreover, there were no differences in LOS, chest tube duration, or postoperative complications between the two groups. Overall, our outcomes are in-line with recently published experiences^[6,8,18,19].

Ultimately, we did not find a difference in the rate of postoperative PAL or chest tube duration between the two groups. While a recent analysis of the Society of Thoracic Surgeons DataBase reported an overall rate of PAL of 10.4%^[20], rates following anatomic lung resection range from 6% to 30%^[19]. Several risk factors have been reported to increase the risk of PAL, including forced expiratory volume in 1 second $< 70\%$ of predicted, body mass index $< 25 \text{ kg/m}^2$, previous smoking, anatomic lung resection, pleural adhesions, male sex, and right upper lobe procedure^[19,20]. Many of our patients have several, if not most of these risk factors. In addition, our rural patient population has a significant proportion of patients who began smoking at an early age. Smoking in childhood and during the teenage years can slow lung development and increase the risk of chronic obstructive pulmonary disease in adulthood^[21]. Early smoke exposure leads to airway inflammation and parenchymal lung injury with larger saccules, increased density of interstitial tissue, and reduced elastin and collagen^[22]. These factors may help to explain our rate of postoperative PAL in the setting of otherwise low rates of complications. However, our study is not powered or intended to predict an increase in PAL based on these factors. In addition, we are aggressive about discharging patients from the hospital with a chest tube in place. Given our rural catchment area, this may result in some delay in actual chest tube removal beyond Postoperative Day 5 when an air leak is not actually present.

Variability in the techniques of robotic anatomic lung resection exist. A recently published survey of high-volume robotic thoracic surgeons demonstrated that most respondents utilized a four-arm approach and 94% used an additional non-robotic assistant port^[23]. In respondents, there was not a universal standard port placement, and stapling port strategies were nuanced by lobe and type of stapler used. As additional technologies are developed, it will be important to evaluate their efficacy and effectiveness, in terms of both clinical outcomes and healthcare costs.

The successful performance of robotic lung resection requires a strong team in the operating room composed of surgeons, nurses, surgical techs, anesthesia providers, and a bedside assistant. The literature describes the learning curve of a robotic lobectomy as 18-32 cases for a surgeon and 20 for a bedside assistant^[24-26]. Specific to anatomic lung resection, division of the pulmonary vascular structures is a potentially hazardous portion of the operation that requires significant skill to perform safely. Prior to the development of the robotic stapler, this required a competent bedside assistant or the console surgeon to return to the bedside. At our institution, we have dedicated physician assistants or trained residents who can safely complete these tasks. However, this may not be the case for every thoracic surgeon. Others have fully described the range of motion capabilities of the EndoWrist® stapler, as well as the safety components that ensure adequate closing and prevent the firing of an incorrectly loaded or spent reload^[8]. Drawbacks of using the robotic stapler are the need for a 12-mm port, the long length of the stapler load that can impede maneuverability in the chest, and the rotational limitation that can occur when the wrist is fully flexed. This stapler does provide the console surgeon with the ability to control the stapler during division of critical structures and may improve one's ability to perform complex minimally invasive techniques with reduced conversions^[9,17]. These benefits may be more apparent at sites where a fully thoracic-trained bedside assistant is not available.

The findings of our study should be viewed in the context of several limitations. This is a retrospective, single institution cohort study and subject to potential selection bias, and our results may not be generalizable to other patient populations. In addition, our data show that the robotic stapler group operating time was significantly longer. However, as mentioned above, this is likely related to one surgeon's learning curve and not an inherently longer time for use of the stapler. Nevertheless, our outcomes are in-line or better than those reported by multiple authors in the literature, and, to our knowledge, this is the first study to directly compare the EndoWrist® robotic stapler to a traditional Endo GIA™ stapler. Clinical outcomes appear to be equivalent in our patient population and further study is needed to assess if there is a difference in cost-effectiveness between these devices.

In conclusion, robotic anatomic lung resection has been shown to be safe and feasible with equivalent long-term oncologic outcomes when compared to VATS and thoracotomy. In this study, we compared perioperative outcomes of patients undergoing robotic anatomic lung resection to assess whether there are any differences based on the type of stapler utilized. We found equivalent rates of complications, PAL, and chest tube duration between the two groups. Based on our data, we recommend that surgeons use the stapling device with which they are most confident.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Phillips JD, Fay KA, Finley DJ

Made substantial contributions to data interpretation and drafting and critical revisions of the manuscript: Phillips JD, Fay KA, Hasson RM, Millington TM, Finley DJ

Availability of data and materials

The data source is a prospectively collected institutional database containing personal health information (PHI). Per Dartmouth-Hitchcock Medical Center (DHMC) policy, any request for data would require an approved Data Use Agreement (DUA) between DHMC and the requesting individual and/or institution.

Financial support and sponsorship

None.

Conflicts of interest

Phillips JD has previously received consulting fees from Intuitive Surgical, Inc. but has no ongoing relationship. All other authors declared that there are no conflicts of interest related to this work.

Ethical approval and consent to participate

The study was reviewed by the Committee for the Protection of Human Subjects of Dartmouth-Hitchcock Medical Center and approved.

Consent for publication

Not applicable.

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Review

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Nodal upstaging robotic lobectomy for non-small cell lung cancer

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Abstract

Nodal upstaging takes place when unsuspected lymph node metastases are detected by pathological evaluation, after surgical treatment for non-small cell lung cancer. In early stages non-small cell lung cancer, nodal upstaging amounts to 4.8%-24.6%, depending on several factors, such as accuracy of preoperative staging, localisation and size of tumour and number of lymph nodes removed. Nodal upstaging is considered a surrogate of the completeness of thoracic oncologic surgery; for this reason, various studies focus on the evaluation of its rate in the different surgical approaches used to treat lung cancer. In this analysis, a high percentage of upstaging is observed in robotic surgery, having similar values to open surgery results, usually considered the gold standard in terms of oncologic radicality. In fact, thanks to its features, robotic surgery allows carrying out a thorough lymphadenectomy in the most comfortable manner, ensuring an excellent vision and manoeuvrability of the instruments even in the most remote areas of the thorax. According to these results, robotic surgery constitutes a safe and radical surgical option, showing encouraging results on the efficacy of lymphadenectomy and, consequently, on its the long-term outcomes.

Keywords: Nodal upstaging, robotic surgery, lung cancer, non-small cell lung cancer, radicality, oncologic outcomes

INTRODUCTION

Nodal upstaging means presence of unsuspected pathologic metastasis in hilar or mediastinal lymph nodes



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Table 1. Nodal upstaging in non-small cell lung cancer

Ref.	Patients	Nodal upstaging (%)	N1 upstaging (%)	N2 upstaging (%)	Nodes removed	Nodal stations examined
Rocha <i>et al.</i> ^[7]	Thoracotomy = 109	16.5		8.3		
Licht <i>et al.</i> ^[1]	Thoracotomy = 796	24.6	13.1	11.5		4.51 ± 1.42
	VATS = 717	11.9	8.1	3.8		4.57 ± 1.34
Decaluwé <i>et al.</i> ^[6]	Thoracotomy = 158	21.5	13.3	8.2		5 ± 1.9
	VATS = 176	10.8	6.3	4.5		5 ± 1.7
Medbery <i>et al.</i> ^[18]	Thoracotomy = 12048	11.9	8.0	3.9	10.71 ± 7.9	
	VATS = 4935	10.1	6.9	3.2	11.57 ± 8.4	
D'Amico <i>et al.</i> ^[19]	Thoracotomy = 245	8.6	4.1	4.5		4.4 ± 1.8
	VATS = 171	8.8	6.4	2.3		4.8 ± 2.12
Reichert <i>et al.</i> ^[20]	VATS = 67	16.9	11.7	5.2	19.57 ± 0.99	
Martin <i>et al.</i> ^[12]	Thoracotomy = 1964	9.9	6.3	3.7		
	VATS = 500	4.8	3.0	1.8		
Boffa <i>et al.</i> ^[9]	Thoracotomy = 7137	14.3	9.3	5.0		
	VATS = 4394	11.6	6.7	4.9		
Toosi <i>et al.</i> ^[3]	Robot = 249	16.4	8.0	8.4	13.9 ± 0.4	5.5 ± 0.1
Wilson <i>et al.</i> ^[13]	Robot = 302	10.9	6.6	4.3	20.9	
Zirafa <i>et al.</i> ^[14]	Thoracotomy = 106	17.9	15.1	2.8	14.32 ± 7.34	4.22 ± 1.58
	Robot = 106	20.8	11.3	9.4	14.42 ± 6.99	4.95 ± 1.2
Lee <i>et al.</i> ^[8]	Robot = 53	13.2	9.4		17 (4-40)	
	VATS = 158	15.2	8.2		11 (1-44)	

VATS: video-assisted thoracic surgery

detected during histopathologic analysis and it is considered synonymous to the radicalness of resection in lung cancer.

The rate of nodal upstaging, reported in non-small cell lung cancer (NSCLC) patients, is variable (10.3%-26.9%), depending on the surgical approach and the clinical stage of the patients considered [Table 1]. Several factors have been reported to influence nodal upstaging in clinical early stages. The dissection of an adequate number of lymph nodes is undoubtedly a fundamental element to take into account, being linked to the risk of lacking metastatic lymph nodes^[1]. Hence, a larger number of assessed lymph nodes results in a better prognosis for lung cancer patients^[2]. Current recommendations indicate that at least three mediastinal stations, as well as hilar nodes should be removed to achieve an appropriate staging^[3]. Moreover, Ismail *et al.*^[4], in their experience with uniportal video-assisted thoracic surgery (VATS) anatomical resection, suggested that 18 lymph nodes is an adequate number to acquire an accurate upstaging rate, in particular 7 hilar nodes appear enough for N1 upstaging and 11 mediastinal nodes for N2 upstaging evaluation.

NODAL UPSTAGING IN NSCLC

In addition, nodal upstaging depends on the characteristic of primary neoplasm; in fact, the dimension of the tumour > 2 cm, clinical T stage > 1, central tumour, localisation in lower lobe and PET with SUV max value > 4 are to be considered risk factors^[5]. The role of histology is debated, given that Decaluwé *et al.*^[6] described an association between squamous cell histology and nodal upstaging, whereas Toker identified the adenocarcinoma as a risk factor for upstaging. Furthermore, Toker recognised the possible influence of some diseases, such as diabetes mellitus, rheumatoid arthritis and tuberculosis, on nodal upstaging^[5].

Accuracy in preoperative staging takes on a crucial role in nodal upstaging. CT scan and PET should be carried out in all patients, in association with endoscopic diagnostic procedures (EBUS) or mediastinoscopy in doubtful cases. Despite a thorough clinical staging, unsuspected node metastasis

is observed in about one-third of the patients after surgery. Rocha described a N2 upstaging in 8.3% of patients with preoperative negative nodes, investigated by mediastinoscopy^[7].

The last element that may obviously affect the quality of lymphadenectomy is the surgical technique^[8]. Specifically, the dissection of nodes in the hilum seems to be directly related to the surgeon's experience and, consequently, nodal upstaging represents a surrogate for expertise in a specific surgical approach^[9]. This is confirmed by the variability of results about the lymphadenectomy in the different studies, which show higher upstaging rate in more experienced facilities.

The role of the various surgical tools is to facilitate the operation, allowing to perform high-quality surgical procedures, in a safe and comfortable manner. VATS has represented a lucky break in lung cancer therapy, allowing to treat patients with a less traumatic approach. VATS is yet strongly dependent on surgeon's technical skills, resulting in some level of discrepancy in the quality of the surgery. Robotic surgery with its technological features embodies the minimally invasive approach and the possibility to carry out the operation versatily, overcoming potential difficulties.

Over the latest years, papers have focused the attention on lymphadenectomy and nodal upstaging in order to evaluate the quality of minimally invasive surgery (MIS), compared to open surgery in the treatment of lung cancer. Video-assisted thoracic surgery and the most innovative robotic surgery are associated with better postoperative results, in terms of length of stay, rate of complications and quality of life^[10,11]. Nevertheless, due to their most recent introduction in daily practice, data on long-term outcomes in lung cancer patients who underwent MIS are bounded. For this reason, the analysis of nodal upstaging rate has become a fundamental element to evaluate the completeness of surgical resection provided by minimally invasive technique, in comparison with the more established open approach.

Initial studies have discussed the quality of lymphadenectomy in patients with clinical early NSCLC who underwent VATS and thoracotomy. The results of the comparison between these two techniques are discordant. Despite the number of nodal stations resected being similar, in the group of patients treated by VATS, a lower upstaging rate was observed when compared to the other group. Decaluwé *et al.*^[6] reported an overall nodal upstaging in 15.9% of clinical stage I patients, with a substantially lower rate in VATS group, although there was no difference in the global number of dissected nodal stations (in the open group: 5 ± 1.9 ; in the VATS group: 5 ± 1.7 ; $P = 0.99$). Licht, in his analysis of 1513 lobectomy of Danish registry, observed nodal upstaging in 18.6% of cases, with a higher percentage in open than VATS group. In particular, N1 upstaging was 13.1% in open lobectomy and 8.1% in VATS lobectomy, whereas N2 upstaging was 11.5% in open group and 3.8% with VATS approach. In contrast with the lower percentage of nodal upstaging reported in VATS resections, the overall survival results superior in patients treated by the minimally invasive approach^[1]. In fact, VATS seems to be associated with an improvement of survival in pathologic stage I, probably due to the reduction of complications and consequent higher early-survival in elderly and compromised patients^[12]. The divergence in nodal upstaging is probably caused by various factors. One of them is surely represented by the selection of the patients, as bigger and central lesions are not usually selected for MIS. In addition, the surgical technique can influence the quality of resection obtained by VATS procedures and the surgeon's experience in minimally invasive surgery and the use of fissureless technique have a particular impact over the result obtained, evading the N1 dissection located in the interlobar site.

NODAL UPSTAGING EVALUATION IN ROBOTIC SURGERY FOR LUNG CANCER

More recently, the surgeon's assessment has focused on robotic surgery and its oncologic long-term outcomes. In 2015, Lee *et al.*^[8] described similar upstaging in VATS and robotic groups, with a trend of a

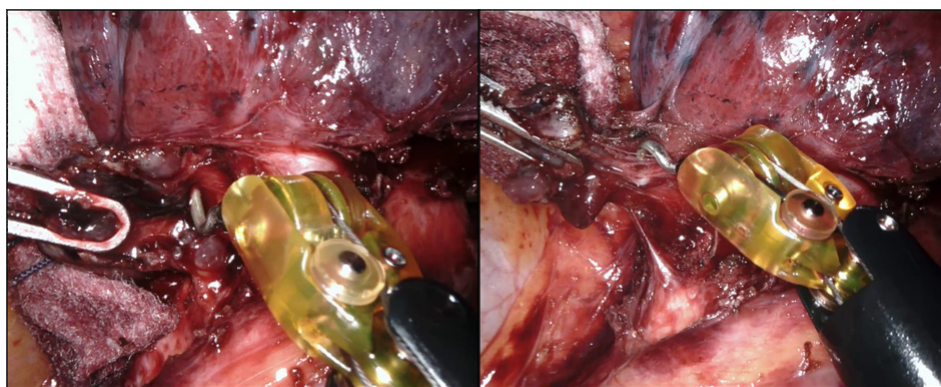


Figure 1. Hilar lymphadenectomy during robotic left upper lobectomy in a patient who underwent neoadjuvant chemotherapy

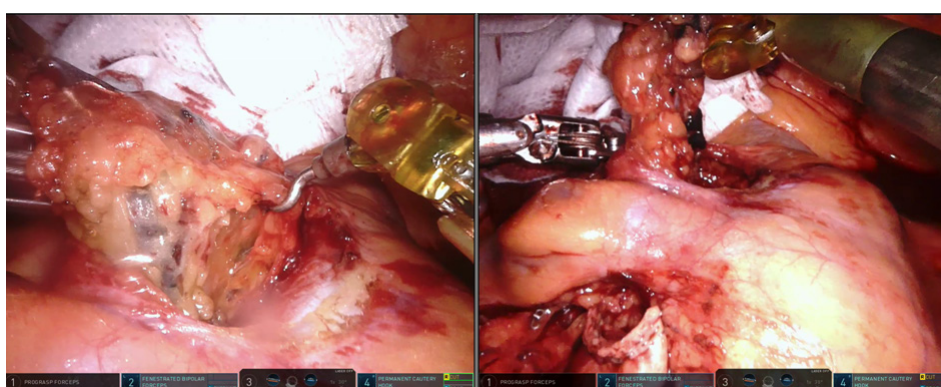


Figure 2. Mediastinal lymphadenectomy (4R station) during robotic right upper lobectomy

higher rate of unsuspected metastasis in hilar nodes by robotic surgery. Different results were reported by Wilson *et al.*^[13], who evaluated 302 clinical stage I NSCLC patients treated by robotic segmentectomy or lobectomy. He reported nodal upstaging in 10.9% of cases, from N0 to N1 in 6.6% and to N2 in 4.3%. These results are in line with the nodal upstaging rate recorded with the open approach, which is considered the gold standard approach^[13]. Indeed, in the hands of an expert surgeon, robotic surgery would enable the possibility to resect with higher precision the lymph nodes, resulting in a more accurate staging, as described by Toosi *et al.*^[3]. In fact, in his evaluation of robotic lymphadenectomy during lobectomy for NSCLC, Toosi *et al.*^[3] observed a mean number of total dissected nodes (N1 + N2) of 13.9 ± 0.4 , with a mean of N2 nodes of 7.7 ± 0.3 and an assessment of at least three mediastinal stations in 98.4% of cases. The opportunity to achieve a more thorough lymph node dissection, with a higher completeness, using robotic surgery was confirmed by a study comparing between robotic and open lobectomy for clinical N0 NSCLC, with a total number of dissected nodes of 14.42 ± 6.99 in robotic and of 14.32 ± 7.34 in open group. In this study, the percentage of nodal upstaging in the two groups was similar, 20.8% by robotic surgery and 17.9% by open approach, confirming that lymphadenectomy by robotic approach can be precise, equalling open surgery^[14]. Studies about oncologic outcomes after lung resection have confirmed the suitability in terms of oncologic radicality of resection of the robotic surgery for NSCLC treatment. According to Louie, robotic approach assures a similar five-year survival and lymph nodes staging to open approach, with shorter hospitalization, less pain, faster recovery and reduced impact on pulmonary function^[15]. These results are in line with other studies regarding the application of robotic approach, also in more advanced lung cancer stages, which reported data conforming to open surgery. In our experience, in the analysis of 212 NSCLC cases who underwent major lung resection by robotic surgery, the actuarial overall survival was 98.5% for stage I, 93.7% for stage II, 73.1% for stage III and 0% for stage IV, at 60 months^[16]. Toosi *et al.*^[3] reported a

three-year overall survival of 75%, 73%, 44% and 0% for pI, pII, pIII and pIV, respectively. In a multicentric study, Cerfolio *et al.*^[17] described five-year stage-specific survival of 83% for stage IA, 77% for stage IB, 68% for stage IIA, 70% for stage IIB, 62% for stage IIIA (including N2 disease patients) and 31% for stage IIIB, to confirm the high quality of the surgical robotic resection.

The recent literature and the increasing diffusion of minimally invasive approaches worldwide in thoracic field are proclaiming robotic surgery as the present as well as the future in the treatment of lung cancer.

Currently, despite the lack of haptic feedback, featuring the current system (DaVinci, Intuitive Surgical, Sunnyvale, CA), robotic surgery allows proceeding comfortably and safely during the dissection of lymph nodes. In fact, the scaled motions, the dexterity, the high geometrical precision and the instrument's wide range movement support the surgeon during the lymphadenectomy, making it easier to reach all the hilar and mediastinal stations without difficulties [Figures 1 and 2]. In addition, taking advantage of the high definition 3D camera with the 10-fold magnified view of surgical field, the surgeon can perform the dissection of nodes with a greater accuracy, limiting bleeding and other intraoperative complications. Thanks to the robotic system features, skilled robotic surgeons have also been able to approach clinical N2 NSCLC treated by neoadjuvant therapy, obtaining positive results, despite the challenges represented by the tissue rearrangement.

CONCLUSION

Given these results, robotic surgery can constitute an ever more valuable instrument for the surgeons, to offer a radical and safe operation with minimally invasive approach, also in advanced stage NSCLC or in complex cases.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Zirafa CC

Performed data acquisition, as well as provided administrative, technical, and material support: Romano G, Nesti A, Davini F, Melfi F

Availability of data and materials

Not applicable.

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Conflicts of interest

Prof. F Melfi is an official proctor for Intuitive Surgical. The other authors have no conflicts of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Robotic selective thoracic sympathectomy for hyperhidrosis

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Abstract

Aim: Thoracic sympathectomy is indicated in patients with upper extremity hyperhidrosis. The success of dorsal thoracic sympathectomy is judged by the rates of relief of hyperhidrosis, recurrence, and compensatory hyperhidrosis. We studied robotic selective sympathectomy (RSS) directed at the division of the preganglionic and postganglionic rami without interruption of the sympathetic chain.

Methods: During RSS, the preganglionic and postganglionic sympathetic fibers and communicating rami to intercostal nerves 2, 3, and 4 are divided. The sympathetic chain is left intact.

Results: Forty-seven patients underwent RSS. RSS was performed in a staged fashion with the more symptomatic side first, followed by the contralateral side after at least four weeks. Mean operative time was 67 ± 13 min for unilateral RSS. There was no conversion to thoracotomy. The mean increase in ipsilateral palmar temperature was 1.2 ± 0.3 °C. Median hospital stay was three days (range 1-4 days). Complications included transient heart block after sympathectomy on the second side in 1/47 (2%) and transient partial Horner's syndrome which resolved in two weeks in 1/47 (2%). There was no permanent Horner's syndrome. Relief of hyperhidrosis was seen in 98% of patients. At a mean follow up of 28 ± 6 months, 46/47 (98%) patients were free of sustained compensatory hyperhidrosis.

Conclusion: RSS is associated with excellent relief of hyperhidrosis and the lowest reported rate of compensatory hyperhidrosis.



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Keywords: Robotic, sympathectomy, hyperhidrosis, minimally invasive, selective sympathectomy

INTRODUCTION

Surgery on the sympathetic nervous system is characterized by the evolution of indications and techniques which have correlated with the evolution and greater understanding of the physiology and anatomy of this complex part of the nervous system^[1-20].

Presently, hyperhidrosis is the most important established indication for sympathectomy. Historically, surgical sympathectomy for hyperhidrosis has been associated with three areas of controversy: (1) the surgical approach; (2) the technique of sympathectomy; and (3) the extent of sympathectomy.

Many surgical approaches have been described: (1) the posterior thoracic approach; (2) cervical supraclavicular approach; (3) transthoracic approach; (4) trans-axillary approach; (5) thoracoscopic approach; and (6) robotic thoracoscopic approach. Sympathectomy can be accomplished by: ganglionectomy, clipping, or ablation of the dorsal sympathetic chain.

The extent of sympathectomy correlates with the incidence of complications. Clearly, more limited sympathectomy has been associated with lower rates of compensatory hyperhidrosis. Although there is no definite consensus, it has been suggested that highest success rates occur when interruption is performed for T3 and T4 for palmar hyperhidrosis. T4 and T5 interruption is recommended for palmar and axillary, palmar, axillary, and pedal hyperhidrosis. T3 interruption has been recommended for craniofacial hyperhidrosis^[21].

Selective postganglionic sympathectomy represents a more directed approach to sympathetic denervation of the upper extremity^[22]. In this procedure, the sympathetic trunk and ganglia are left intact and only the postganglionic rami, which accompany the intercostal nerves 2, 3, and 4 to the upper extremity, are divided selectively. Friedel *et al.*^[23] reported a success rate of up to 95% and a compensatory hyperhidrosis rate of 2.5% after performing selective postganglionic sympathectomy or ramicotomy. Recently, Coveliers and colleagues reported a series of patients who underwent robotic simultaneous bilateral selective dorsal postganglionic ramicotomy using a surgical robot^[24,25]. Although postganglionic ramicotomy has been used for more than 20 years, most surgeons have abandoned the technique because studies have found a significantly higher recurrence rate in comparison with sympathectomy^[26-29]. It has been suggested that the historic results with ramicotomy may have been in part due to the limitations of the visualization and instrument technology, and the fact that the preganglionic fibers were left intact.

Given the theoretical advantage of reducing compensatory sweating by limiting the extent of sympathectomy, we have reasoned that the division of both the preganglionic and postganglionic rami communicantes from the sympathetic trunk to the upper extremity without targeting the trunk itself may be a more effective technique for “selective sympathectomy”.

This paper outlines the technique of robotic selective sympathectomy (RSS) and the early results.

METHODS

Technique

A left-sided double lumen tube is used and the lung on the side of the procedure is isolated. The patient is placed in a lateral decubitus position.

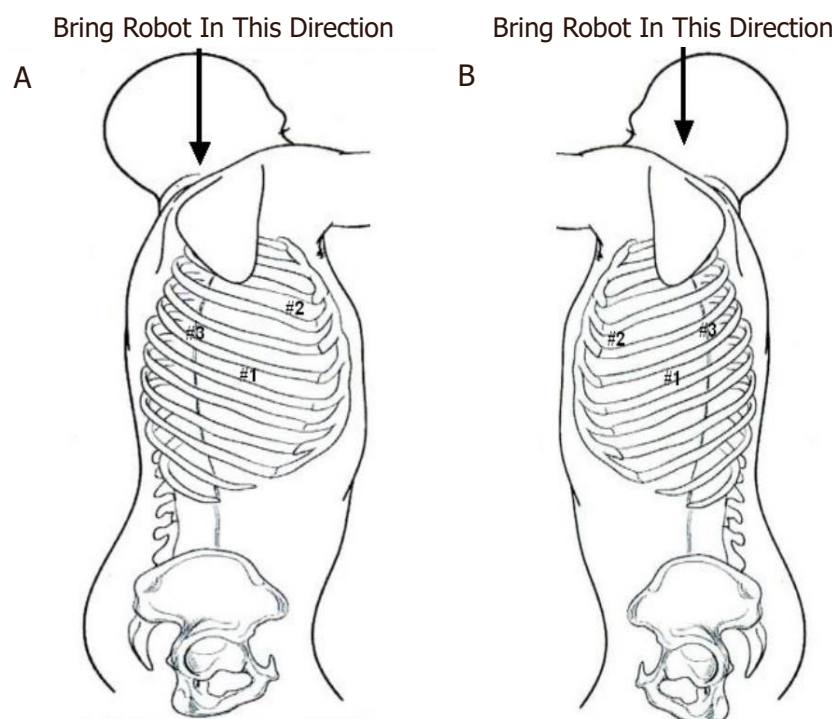


Figure 1. Port placement during robotic selective dorsal sympathectomy. A: right chest; and B: left chest

The robot is brought over the patient's head. We use both da Vinci (Intuitive Surgical Mountainview, CA) Si and Xi robots. For clarity, we refer to the robotic arms not by arm number but in reference to the surgeon's hands. An 8-mm port (#1) is placed in the sixth intercostal space in the midaxillary line [Figure 1A and B]. A second port (#2) is placed in the third intercostal space in the anterior axillary line. The camera arm with a 30° down-viewing binocular camera is introduced through Port #1. For approach to the sympathetic chain in the right chest Port #2 is used by the right robotic arm, and for the left-sided sympathetic chain Port #2 is used by the left robotic arm. A third port (#3) is placed in the fifth intercostal space in the posterior axillary line. For approach to the sympathetic chain in the right chest Port #3 is used by the left robotic arm, and for the sympathetic chain in the left chest Port #3 is used by the right robotic arm. Carbon dioxide insufflation can be used with the port-based technique. Carbon dioxide is used to retract the lung away from the posterior chest wall. If carbon dioxide insufflation is not used, an auxiliary 10-mm port is placed in the sixth intercostal space in the anterior axillary line. A retractor (Endopaddle Retract Covidien, Inc., Norwalk, Conn. USA) is passed through this port and used to retract the lung medially. In the right chest, the right robotic arm with the robotic hook cautery is positioned through Port #2, and the left robotic arm with the robotic DeBakey forceps is positioned through Port #3. In the left pleural space, the right robotic arm enters the pleural space through Port #3 and the left robotic arm enters the pleural space through Port #2. The sympathetic chain is identified. The ribs are counted and electrocautery marks are placed away from the sympathetic ganglia in order to specify the position of ganglia #2, #3, and #4 [Figure 2]. The portion of the sympathetic chain between ganglia #4 and #5 overlying rib #5 is identified and dissected with the hook cautery. The sympathetic chain is encircled and lifted with a rubber atraumatic vascular loop. The postganglionic fibers (RCG) can be identified easily as the fibers emanating from the chain towards the distal portion of the ribs. These fibers are divided using electrocautery. The preganglionic fibers entering the sympathetic chain are also divided and the chain is elevated. Dissection is carried to the level of the second sympathetic ganglion. Following the division of the preganglionic and postganglionic fibers, the sympathetic chain is elevated and all posterior attachments to the ribs are severed using electrocautery. This maneuver disconnects the rami interganglionares that are communicating fibers between the ganglia.

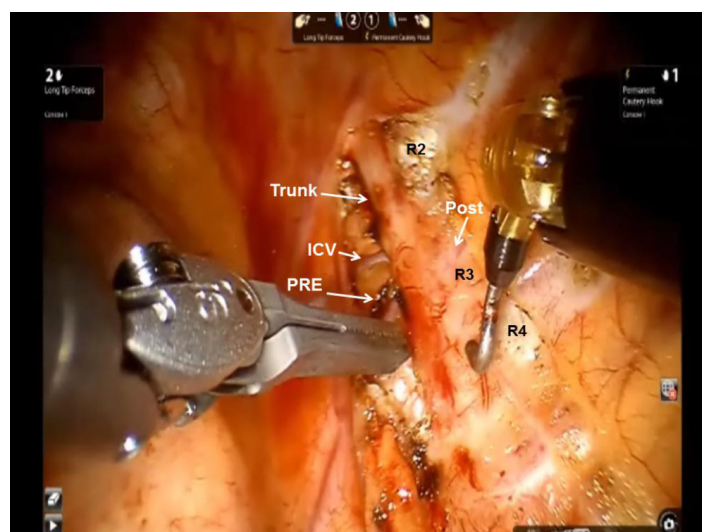


Figure 2. Intraoperative photograph during left robotic selective sympathectomy depicting Ribs 2-4 (R2, R3, and R4), the PRE and Post rami, the Trunk, and an ICV. During “selective sympathectomy” preganglionic and postganglionic rami are divided, and the trunk is left intact. PRE: preganglionic; Post: postganglionic; ICV: intercostal vein; Trunk: sympathetic trunk

Following completion of the highly selective sympathectomy, a flexible drain is positioned posteriorly in the pleural space and brought out through Incision #1. On-Q subpleural catheters are placed traversing T2-T8, as has been described elsewhere in this book for pain control. All patients are extubated and returned to the recovery room.

Video of the procedure can be seen at <https://youtu.be/8NvTznv4Qrg>.

All patients underwent division of R2, R3, and R4 preganglionic and postganglionic rami.

Data analysis

The data were prospectively accrued and retrospectively analyzed. Data points analyzed included indications for operation, patient age and sex, preoperative and postoperative Hyperhidrosis Disease Severity Scale [Table 1], operative time, palmar temperature measurements, morbidity, death, compensatory hyperhidrosis, and gustatory sweating.

Compensatory hyperhidrosis was defined as the presence of new sweating, which was not present preoperatively, in a different part of the body. The presence of compensatory hyperhidrosis and gustatory hyperhidrosis was based on the subjective reporting of the patient.

Relief of symptoms, satisfaction with the operation, and occurrence and intensity of compensatory sweating were evaluated using a standard questionnaire and the Hyperhidrosis Disease Severity Scale. Further follow up was conducted at three months and at one, two, and three years after the operation. At the time of follow up, relief of symptoms, satisfaction with the operation, and occurrence and intensity of compensatory sweating were evaluated using a standard questionnaire and the Hyperhidrosis Disease Severity Scale.

RESULTS

In total, 102 patients underwent RSS. In 55 patients, RSS was performed in a simultaneous bilateral fashion. In 47 patients, RSS was performed in staged fashion with the more symptomatic side first, followed by the contralateral side after at least four weeks. These patients are the subject of this study. In all patients, the

Table 1. Hyperhidrosis disease severity scale

A	Sweating is never noticeable and never interferes with daily activities
B	Sweating is tolerable and sometimes interferes with daily activities
C	Sweating is barely tolerable and frequently interferes with daily activities
D	Sweating is intolerable and always interferes with daily activities

indication was axillary and palmar hyperhidrosis. Mean operative time was 67 ± 13 min for unilateral RSS. There was no conversion to thoracotomy. The mean increase in ipsilateral palmar temperature was 1.2 ± 0.3 °C. Median hospital stay was three days (range 1-4 days). Chest tube was removed on the first postoperative day (POD#1) in 43/47 (92%) patients and the second postoperative day (POD#2) in 4/47 (8%) patients. There were no bleeding complications. Complications included transient heart block after sympathectomy on the second side in 1/47 (2%) and transient partial Horner's syndrome that resolved in two weeks in 1/47 (2%). There was no permanent Horner's syndrome.

Whereas all patients had a score of D preoperatively, at a mean follow up of 28 ± 6 months, 46/47 patients had a score of A. The overall sustained resolution of hyperhidrosis was 98%. In one patient (2%), hyperhidrosis recurred in the first operated side after three months.

Compensatory hyperhidrosis was seen in 19/47 (40%) patients after selective dorsal sympathectomy of the dominant upper extremity. The contralateral selective dorsal sympathectomy was delayed until the resolution of the transient compensatory hyperhidrosis, which occurred within four weeks in all patients. Transient compensatory hyperhidrosis was seen in 21/47 (45%) after selective dorsal sympathectomy of the contralateral upper extremity. This resolved in 46/47 patients within five weeks after the procedure. At a mean follow up of 28 ± 6 months, 46/47 (98%) patients were free of sustained compensatory hyperhidrosis. One patient (2%) experienced compensatory hyperhidrosis affecting the anterior abdomen and lower chest. There was no gustatory sweating in this group of patients.

DISCUSSION

The success of dorsal thoracic sympathectomy is judged by: (1) high rate of relief of hyperhidrosis; (2) low rate of recurrence; and (3) low rate of compensatory hyperhidrosis and gustatory hyperhidrosis.

Invariably, surgical procedures achieve symptomatic relief but are associated with compensatory hyperhidrosis in 50%-97% of patients^[30-33]. Compensatory hyperhidrosis, which occurs on the trunk and lower extremities following sympathectomy and gustatory hyperhidrosis and refers to facial sweating associated with eating or olfactory sensation of hot spicy food, is a significant complication of sympathectomy. As a result, several studies have attempted to determine whether limiting the extent of sympathectomy can impact the incidence of these two complications^[34-40]. However, the results have been inconsistent and randomized trials have not been performed. In 2000, Furlan *et al.*^[41] reviewed published series after sympathectomy. They reported a compensatory hyperhidrosis rate of 52.3%, gustatory hyperhidrosis rate of 32.3%, phantom hyperhidrosis of 38.6%, and Horner's syndrome in 2.4% of patients. In 2200 patients undergoing ablation of T2 ganglion for palmar sweating and T3-T4 ganglia for axillary sweating, Lin and associates showed successful sympathectomy in 99% of patients^[42]. However, compensatory hyperhidrosis was noted in 88% of patients. From these studies, a number of conclusions can be reached: (1) longer extent of dorsal thoracic sympathectomy is associated with greater risk of compensatory hyperhidrosis; (2) the severity of compensatory hyperhidrosis is decreased with staging of dorsal sympathectomy with unilateral sympathectomy accomplished a few weeks apart versus bilateral sympathectomy at the same setting; (3) the extent of compensatory hyperhidrosis is decreased with selective ramicotomy; and (4) incidence of Horner's syndrome is lower with transthoracic approach when

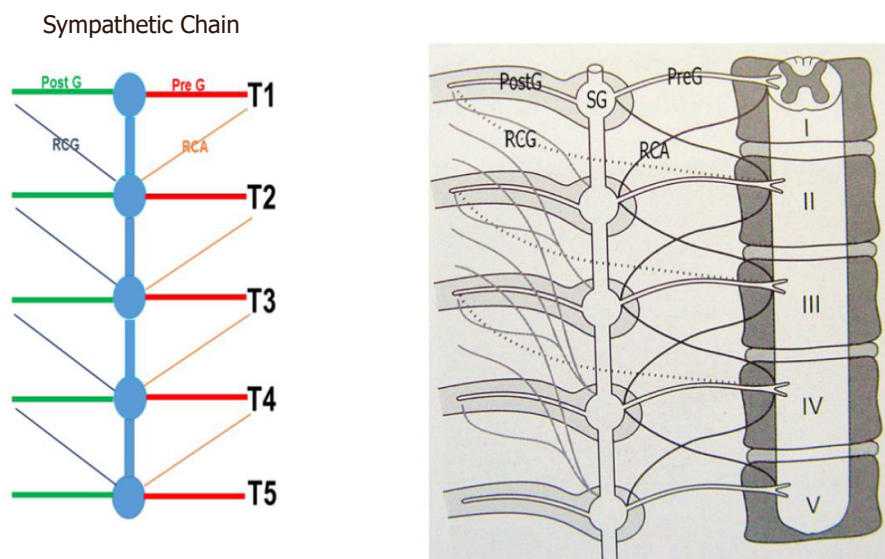


Figure 3. Sympathetic chain from T1 to T5. PreG fibers from the spinal cord synapse within the SG and PostG fibers travel with the intercostals nerves. The RCA connect the corresponding spinal nerves with the ganglia of the sympathetic chain. The RCG connect within the sympathetic chain with the RCA and proceed to the peripheral organs. PreG: Preganglionic; SG: sympathetic ganglion; PostG: postganglionic; RCA: rami communicantes albi; RCG: rami communicantes grisei

sympathectomy is performed by dissection versus diathermy of the T2 ganglion or when sympathectomy is limited to below the T2 ganglion.

Landmark studies by Wittmoser and later by Friedel have determined the ideal extent of sympathectomy. Friedel *et al.* [23] studied three possible techniques for selective sympathectomy: (1) thoracic resection of the sympathetic chain including T2-T4 ganglia and intervening trunk. They referred to this technique as interganglionare. They concluded that this technique results in compensatory hyperhidrosis in the majority of patients. With this technique, Horner's syndrome is seen in a smaller percentage of patients compared to thermal ablation. The shortcoming of this technique is the possibility of leaving the postganglionic RCG with resultant less than complete sympathectomy [Figures 3 and 4]; (2) division of the preganglionic rami communicantes albi (RCA) [Figure 5]; and (3) division of preganglionic, and postganglionic fibers as well as RCG and RCA for T2-T4 [Figure 6].

Using the technique of selective sympathectomy with the division of the postganglionic RCG for T2-T4, these authors showed relief of axillary hyperhidrosis in all of their patients. Furthermore, with this technique, they did not report any patients with Horner's syndrome. Finally, this technique has resulted in the lowest reported rate of compensatory hyperhidrosis (16%).

It has been postulated that limiting the extent of sympathectomy or sympathicotomy may decrease the rate of compensatory hyperhidrosis. The thoracic sympathetic chain is composed of both nerve bodies of the second sympathetic neuron as well as postganglionic axons from nerve bodies from other levels that travel within the chain. Microscopic examination of what macroscopically appears as a ganglion in the sympathetic chain reveals a combination of nerve bodies as well as communicating axons from other nerve bodies that travel up and down the chain. Based on this understanding, division of a single macroscopic ganglion does not result solely in the removal of the nerve bodies to that specific level, but also results in the division of the axons from nerve bodies from other levels which travel through the chain. This realization may explain the variability of the extent of sympathectomy when the chain is divided or specific macroscopic ganglia are removed.

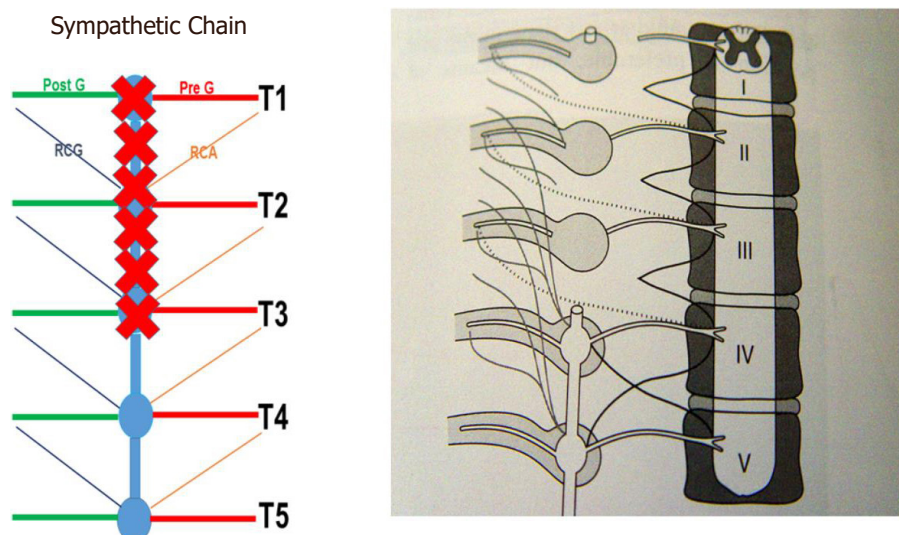


Figure 4. Classic gangliectomy sympathectomy. PreG: Preganglionic; PostG: postganglionic; RCA: rami communicantes albi; RCG: rami communicantes grisei

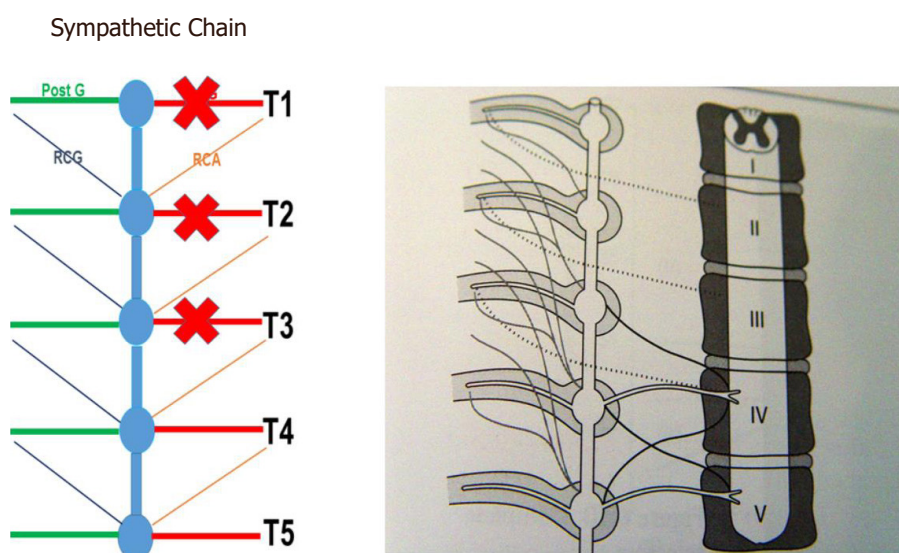


Figure 5. Preganglionic sympathectomy. PreG: Preganglionic; PostG: postganglionic; RCA: rami communicantes albi; RCG: rami communicantes grisei

Selective postganglionic sympathectomy represents a more directed approach to sympathetic denervation of the upper extremity. In this procedure, the sympathetic trunk and ganglia are left intact and only the rami that accompany the intercostal nerves 2, 3, and 4 to the upper extremity are divided selectively.

Friedel *et al.*^[23] reported a success rate of up to 95% and a compensatory hyperhidrosis rate of 2.5% after performing selective postganglionic sympathectomy or ramicotomy by thoracotomy. However, subsequent studies with longer follow up showed that the results were transient and that the long-term compensatory hyperhidrosis rate with this technique was 60%-70%, comparable to other techniques. It has been suggested that the lack of sustained results with this technique was the result of poor visualization of the rami, incomplete ramicotomy, and division of only the postganglionic rami.

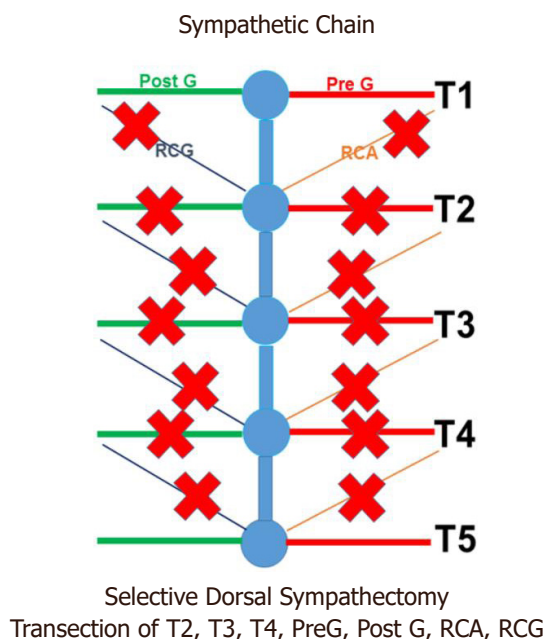


Figure 6. Selective dorsal sympathectomy with division of both preganglionic and postganglionic rami. PreG: Preganglionic; PostG: postganglionic; RCA: rami communicantes albi; RCG: rami communicantes grisei

Selective sympathectomy is not easily accomplished with conventional video-assisted thoracic surgical techniques. The improved dexterity and three-dimensional visualization used with robotic technology makes robotics ideal for selective dorsal thoracic sympathectomy. Using robotic technology and taking advantage of the three-dimensional high resolution magnified view and improved instrument maneuverability in the confined space, Coveliers *et al.*^[24,25] reported a series of patients who underwent simultaneous bilateral selective dorsal postganglionic sympathectomy who after a two-year follow up had a 96% rate of relief of hyperhidrosis and a 7.2% rate of compensatory sweating.

Given the theoretical advantage of reducing compensatory sweating by limiting the extent of sympathectomy, we have reasoned that the division of both the preganglionic and postganglionic rami communicantes from the sympathetic trunk to the upper extremity without targeting the trunk itself may be a more effective technique for “selective sympathectomy”. Furthermore, as compensatory hyperhidrosis after sympathectomy is believed to result from redirection of sympathetic activity to other parts of the body, and has been shown to be related to the extent of sympathectomy, staged bilateral robotic sympathectomy of one upper extremity followed by the other may result in even lower levels of compensatory hyperhidrosis.

In this study, patients with combined axillary and palmar hyperhidrosis underwent RSS in a staged fashion. The staged approach was chosen to allow for the transient compensatory hyperhidrosis to dissipate before further interruption of the sympathetic flow. In addition, given the morbidity associated with the robotic ports, a staged bilateral approach was chosen to obviate bilateral thoracic pain. Presumably due to the use of three robotic ports, optimal pain management necessitated longer hospital stay.

The use of robotic technology adds more ports and results in greater morbidity, longer operative times, and greater cost. These shortcomings may be offset by greater accuracy of dissection and lower rates of compensatory hyperhidrosis.

A randomized, prospective trial comparing this approach with other conventional approaches needs to be performed to further validate the results.

In conclusion, robotic technology has the potential of accomplishing highly selective dorsal preganglionic and postganglionic sympathectomy with accuracy. This technique may decrease the incidence of post sympathectomy compensatory hyperhidrosis and Horner's syndrome.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Vitamin deficiencies and prevention methods after bariatric surgery

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Abstract

Bariatric surgeries have proven to be an effective treatment for morbid obesity to reduce the excess body weight of the individuals. Besides weight loss and improvement in metabolic parameters, bariatric surgery procedures can also cause some complications. One of the most common complications observed after bariatric surgery is vitamin deficiencies. Vitamin deficiencies occur due to malabsorptive surgery in patients with absorption disorder and restrictive surgery in patients with inadequate intake. These deficiencies may be accompanied by systematic and neurological findings. Therefore, regular follow-up of patients after bariatric surgery is crucial. If any vitamin deficiency is detected in the patient clinically or biochemically, it is recommended to eliminate this deficiency through supplementation.

Keywords: Obesity, bariatric surgery, vitamin deficiency, supplementation

INTRODUCTION

Obesity is a public health problem characterized by excessive fat accumulation in adipose tissue resulting from the complex relationship among the genetic, socioeconomic, and cultural factors and the imbalance between energy intake and expenditure^[1,2]. Especially morbid obesity [body mass index (BMI) ≥ 40 kg/m²] adversely affects the quality of life of the individual and is associated with many chronic diseases^[3,4].

In recent years, there has been an increase in the frequency of application of bariatric surgical methods due to the increase in the prevalence of morbid obesity, raising public awareness regarding obesity, and



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improvements in surgical procedures^[5,6]. The goal of bariatric surgery, which is an effective treatment for morbid obesity, is to achieve weight loss in the patient and improve his/her quality of life^[5].

Bariatric surgery methods are classified as restrictive, malabsorptive, and combined methods according to the effect mechanism. In restrictive methods, a small gastric sac is created to limit the amount of food the patient can consume at one time. In malabsorptive methods, a part of the small intestine is bypassed and consequently the absorption of nutrients decreases. In combination methods, both mechanisms are used to achieve weight loss^[7].

Several studies have shown that bariatric surgical procedures ensure weight loss and improvement in metabolic parameters in morbidly obese individuals^[8-10]. However, these individuals need to be evaluated for long-term complications of the surgery^[11]. One of the most common complications after bariatric surgery is vitamin deficiencies. Vitamin deficiencies have been observed in patients who underwent malabsorptive surgery due to absorption disorder and in patients who underwent restrictive surgery due to inadequate intake^[12].

In a study conducted on subjects during the first year following a Roux-en-Y gastric bypass (RYGB), which is a malabsorptive method, vitamin A deficiency in 11% of patients, vitamin C deficiency in 34.6% of patients, vitamin D deficiency in 7% of patients, thiamine deficiency in 18.3% of patients, riboflavin deficiency in 13.6% of patients and vitamin B12 deficiency in 13.6% of patients were found^[13]. Similarly, in another study, in the first year following RYGB, vitamin D deficiency in 12% of patients, vitamin B12 deficiency in 60% of patients, and folic acid deficiency in 47% of patients were determined^[14].

Literature data show that patients who have undergone bariatric surgery are at risk for vitamin B12, thiamine, folic acid, and vitamin A, D, and K deficiency^[15-19]. These deficiencies in patients can be observed in a wide range together with systematic and neurological findings. Therefore, regular monitoring of vitamin levels as well as initiating supportive treatment in the case of deficiency is very important^[20].

This review aims to provide information about vitamin deficiencies seen after bariatric surgeries and prevention methods in the light of the literature.

WATER-SOLUBLE VITAMINS

Thiamine

It is reported that thiamine deficiency, which usually occurs within 4-6 weeks after surgery, is observed in approximately 30% of patients^[12]. For this reason, the European Federation of Neurological Societies recommends postoperative monitoring of the thiamine levels of patients for at least 6 months and, where necessary, performing parenteral thiamine supplementation^[21].

A 100-mg oral thiamine supplementation twice a day is the standard treatment for thiamine deficiency. Patients with symptoms of Wernicke's encephalopathy or acute psychosis need to be kept under medical surveillance in the hospital. These patients should receive at least 250 mg/day thiamine intramuscularly or intravenously for 3-5 days^[20,22,23]. If thiamine deficiency after bariatric surgery cannot be treated with oral thiamine supplementation, it is associated with excessive bacterial growth in the small intestine. Antibiotic treatment is needed to overcome this deficiency, which is called bariatric beriberi^[15].

Riboflavin

Biochemical rather than clinical riboflavin deficiency was reported after bariatric surgery^[13]. If there are findings associated with riboflavin deficiency such as dermatitis, stomatitis, and glossitis in patient, and riboflavin deficiency is also observed biochemically, riboflavin deficiency should be eliminated with 5-10 mg/day oral riboflavin supplementation^[20,23,24].

Folate

Folate acts as a cofactor in the synthesis of methionine, thymidine, and purine nucleotides. Folate deficiency, which occurs as a result of not eating a sufficient and balanced diet, is associated with anorexia, weight loss, and weakness in individuals^[20,24,25]. After bariatric surgery, an average of 38% of patients are reported to have folate deficiency and this deficiency progresses asymptotically^[12]. In the study conducted by Gudzone *et al.*^[14], vitamin D, iron, vitamin B12, and folate levels were evaluated in the first year after RYGB. The prevalence of folate deficiency was reported to be 13% in the first year following the operation in patients who underwent RYGB. In this study, it was emphasized that preoperative and postoperative micronutrient levels of patients were not evaluated and micronutrient deficiencies were common in the evaluated parameters.

Folate deficiency can be treated with 1-5 mg/day oral folic acid supplementation^[20,23,24].

An increase in serum folic acid levels after bariatric surgery is indicative of excessive bacterial growth in the small intestine. This is because some bacteria present in the intestinal flora are capable of synthesizing folic acid^[25]. Excess bacterial proliferation in the small intestine is a disorder observed frequently after the bariatric surgery that changes the intestine structure^[26]. Therefore, patients should also be evaluated for the intestinal malabsorptive disease after bariatric surgery^[24].

Vitamin B12

Vitamin B12 deficiency is quite common in older individuals, vegetarians, pregnant women, and people with kidney or intestinal disease^[27]. After bariatric surgery, vitamin B12 deficiency was observed in 4%-62% of patients and it was argued that the deficiency occurred mostly due to duodenal bypass^[12,24,28]. A selective literature review was performed by Weng *et al.*^[29], who reported that preoperative vitamin B12 prevalence was 2.3% and postoperative prevalence in the 12th month after the operation was 6.5%. In another study, 75 patients with a mean age of 49 were studied; weight loss and nutrient deficiencies were evaluated. According to the results of this study, prevalence of vitamin B12 deficiency increased to 61.8% five years after RYGB operation^[28].

Malabsorption and insufficient food intake were reported as the main reasons for vitamin B12 deficiency in patients who underwent bariatric surgery. Additionally, postoperative food intolerance and bacterial overgrowth in the small intestine were also suggested as causes of the deficiency. Reduction of B12 absorption in the distal ileum as a result of the loss of intrinsic factor-secreting cells, gastric acid suppression therapy with H₂-receptor blockers, and the use of proton-pump inhibitors are other pathophysiological mechanisms leading to the development of vitamin B12 deficiency in patients^[29].

Vitamin B12 depots of the liver and kidney may delay postoperative deficiency for up to three years. Therefore, vitamin B12 deficiency can also be observed several years after the operation^[28].

In a study conducted on patients who underwent sleeve gastrectomy (SG), it was reported that, contrary to the literature, serum B12 levels increased significantly in the third postoperative month compared to preoperative data. In this study, 85% of patients reported that they received B12 supplementation and the increase in serum B12 levels was associated with this condition^[30].

Effective treatment methods of vitamin B12 deficiency was reported as orally 500-2000 µg/day B12 support, 1000-3000 µg intramuscular B12 support every six months, 500 µg nasal B12 support once a week, or 500 µg sublingual B12 support once a day^[20,23,28].

Vitamin C

The deficiency of vitamin C was reported to be common in the first year following the RYGB, occurring in 34.6% of patients^[13]. The studies conducted on the subject reported that the deficiency increased in the first year and continued for 2 years following the surgery^[31,32].

It is recommended that vitamin C deficiency, which is observed frequently after bariatric surgery, should be treated with 200 mg/day oral vitamin C supplementation^[20,23,24].

Biotin

Biotin deficiency after bariatric surgery has not been reported in studies examining biotin deficiency after bariatric surgery^[33,34]. A case regarding the loss of sense of taste after SG is reported in the literature. The patient's loss of taste was eliminated by oral biotin supplementation of 20 mg/day for several weeks^[20,23,35].

FAT-SOLUBLE VITAMINS

Vitamin A

Data from the literature suggest that vitamin A deficiency is more common in patients who have undergone biliopancreatic diversion (BPD) and RYGB surgeries in which the duodenal channel was bypassed^[36,37]. The presence of bile and bile acids in this channel was suggested as the cause of this situation. The relative reduction in bile and bile acids is accompanied by the deconjugation of bile acids, which occurs as a result of bacterial overgrowth in the small intestine, and, thus, vitamin A deficiency is observed in patients^[24].

In the studies on the subject, it was also reported that 10%-11% of vitamin A deficiency occurs in the first year following RYGB and BPD^[36,38].

As an initial treatment for vitamin A deficiency, 10,000 international unit (IU)/day vitamin A oral supplementation is recommended. Since β -carotene-related vitamin A toxicity was not reported in the literature, the use of this compound in the treatment of vitamin A deficiency is recommended^[20,23,24].

Vitamin D

Vitamin D deficiency is a condition observed frequently after bariatric surgery that causes bone losses and fractures, thus morbidity in the long term^[39]. After bariatric surgery, decreased absorption areas in the small intestine, pancreatic secretion, and changes in bile distribution are the factors that lead to decreased absorption of vitamin D^[40].

Vitamin D deficiency is also quite common in morbidly obese patients waiting for bariatric surgery. The prevalence of vitamin D deficiency before surgery is reported to be between 54% and 80%. Inadequate vitamin D intake, insufficient exposure to sunlight, and low bioavailability of vitamin D are reported as the reasons for this condition^[40]. In the case of vitamin D deficiency, parathyroid hormone levels increase in order to maintain calcium balance in the body. This secondary hyperparathyroidism effect increases bone resorption and is associated with osteoporosis and osteomalacia in adults^[41]. It is reported in the literature that the prevalence of secondary hyperparathyroidism after bariatric surgery is up to 58%^[42]. Due to the increased incidence of secondary hyperparathyroid syndrome and vitamin D deficiency after surgery, the effect of different surgical procedures on vitamin D levels has been investigated in several studies^[13,43-47].

Studies have shown that vitamin D deficiency is observed only after SG, which is known as a restrictive method^[43,44]. In a study following patients for one year after SG, vitamin D deficiency was found in 39% of patients despite using daily multivitamin support^[43]. In another study, a significant loss in bone mass and bone structure was observed one year following SG^[44].

Vitamin D deficiency was reported to be 7% in the first year following RYGB, which is a malabsorptive method^[13]. This rate was reported to be 65% in the 10th postoperative year and suggested to be due to increased levels of parathyroid hormone^[41].

The prevalence of vitamin D deficiency was determined as 63% in the fourth year after BPD and 73% in the eighth year^[45,46]. In adjustable gastric band surgery, vitamin D deficiency has been reported to be the second most common micronutrient deficiency after iron (Fe) deficiency^[47].

Data from the literature indicate that vitamin D deficiency is observed following many bariatric procedures^[13,42-47]. In these patients, it is known that bone turnover is accelerated in relation to low bone mineral density and this poses a risk for bone fractures. Therefore, it is very important to regularly monitor the vitamin D levels of patients after surgery and, if necessary, provide vitamin D supplementation^[24,48,49].

In the treatment of vitamin D deficiency, 50,000 IU ergocalciferol support once a week for 12 weeks, and then, 1000-5000 IU/day cholecalciferol support is recommended^[20,23]. In patients with osteomalacia, 50,000 IU ergocalciferol should be given once a week and 600,000 IU ergocalciferol supplementation in total should be reached in 12 weeks. However, there is also evidence that high-dose oral vitamin D supplementation causes liver abnormalities and hypercalcemia. Therefore, patient follow-up should be performed regularly during and after supplementation^[24].

Vitamin E

In the study carried out by Cuesta *et al.*^[38], anthropometric measurements and vitamin levels of 178 patients who underwent 116 RYGB and 62 BPD operations were evaluated before and after surgery. In the first year following RYGB, vitamin E deficiency was not found in the patients and the prevalence of vitamin E deficiency was 4.8% in the first year following BPD.

In case of deficiency, 800-1200 IU/day oral vitamin E supplementation was recommended^[20,23,24].

Vitamin K

Vitamin K deficiency was reported to be rare in the short term after RYGB. Nevertheless, in a study in which BPD patients were followed up for 42 months, vitamin K deficiency was determined in 60% of patients^[50].

It is recommended that vitamin K deficiency be treated with either 2.5-25.0 mg/day of vitamin K taken orally or 5-15 mg parenteral vitamin K supplementation taken intramuscularly or subcutaneously^[20,23,24].

CONCLUSION AND RECOMMENDATIONS

One of the most common complications observed in patients after bariatric surgery is vitamin deficiencies. These deficiencies can negatively affect the quality of life, nutritional behavior, and the goals that are desired to be achieved after surgery by causing many biochemical and clinical disorders in patients. Therefore, regular follow-up of patients after surgery is very important. If any vitamin deficiency is detected in the patient biochemically or clinically, relevant vitamin deficiency should be eliminated immediately through supplementation.

It was reported that vitamin deficiencies are more common in malabsorptive surgery methods; therefore, the patient's bariatric surgery procedure should also be considered while applying vitamin supplementation.

In patients who underwent restrictive surgery, adequate and balanced nutrition should be provided after surgery via the nutrition programs prepared by expert dietitians to prevent vitamin deficiency.

In addition, vitamin deficiencies that exist before surgery in patients may get worse after surgery. Therefore, vitamin levels should be evaluated before surgery and if there is deficiency it must be treated before the operation.

DECLARATIONS

Authors' contributions

Did the literature review, summarized the studies on the subject: Küçükkatirci H
Made the studies that are summarized on the subject into an article: Çalapkorur S
Reviewed and approved the final version of the article: Çalapkorur S, Küçükkatirci H

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Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Endoscopic approach for the treatment of bariatric surgery complications

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Abstract

The incidence of bariatric surgery is increasing exponentially. The number of bariatric surgeries performed in the United States has significantly increased in the past decades. Complications of bariatric surgery can present days to years postoperatively. Advances in endoscopic procedures and technology has made it possible to address many complications endoscopically. We describe the most common complications after bariatric surgery and the endoscopic treatment options available to date.

Keywords: Bariatric surgery, advanced endoscopy, intraluminal surgery

INTRODUCTION

Obesity is a public health problem^[1]. The number of bariatric procedures performed in the United States has increased significantly in the past decades^[1,2]. Laparoscopic Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) are the most common bariatric procedures performed^[2,3]. The overall mortality rate of bariatric surgery is < 0.2%, yet the morbidity rate is between 4% and 10% with complications presenting most commonly within the first 30 days after surgery^[2-4]. Some of the postoperative complications may be managed intraluminally using advances in surgical and interventional endoscopy^[2-6].

Complications can be divided into early (< 30 days) or late (> 30 days)^[3,7]. Some can be encountered after any bariatric procedure and others are procedure specific^[3]. The cornerstone for the diagnosis of luminal



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complications after weight loss surgery is esophagogastroduodenoscopy (EGD). Diagnostic and therapeutic EGD should not be delayed for fear of disruption of a fresh anastomosis. Evidence has shown it is safe and cost-effective to perform upper endoscopy in the early postoperative period^[8].

BLEEDING

Acute or early gastrointestinal (GI) hemorrhage usually presents within the first hours to days after surgery and it is often secondary to technical error^[2,3]. Its incidence is 1%-4%^[9]. Although bleeding usually occurs from the submucosal vessels along the staple line at the gastrojejunostomy, jejunojunostomy, or the sleeve staple line, it can occur anywhere along the GI tract. Possible sites of bleeding include the gastric pouch and the gastric remnant, as well as extraluminal, at trocar insertion sites, dissection planes, or mesenteric or omental transection areas^[2-4]. Late bleeding is usually caused by marginal ulceration or erosion (discussed below)^[5,9].

Signs and symptoms of early postoperative bleeding include tachycardia, hemoglobin level drop, hematemesis, or hematochezia^[9]. Hemodynamically stable patients are initially treated non-operatively with fluid resuscitation, close monitoring, proton pump inhibitors (PPIs), and blood transfusion as needed^[2-4,6,9]. For patients who present hemodynamically unstable, further operative or endoscopic procedures are warranted^[2-4].

Different endoscopic treatments are available to manage a bleed: injection of diluted epinephrine or sclerosing agents, application of hemoclips or larger bear claw clips (Over-the-scope-clip, OTSC, Ovesco), thermal therapies (heater probe, mono- and bipolar electrocoagulation, argon plasma coagulation, and laser therapy), and application of hemostatic powder, fibrin, or thrombin glues^[2-6]. Standard endoscopes can reach proximal bleeders in the gastric pouch or the sleeve staple line. For distal bleeders, balloon- or spiral-assisted enteroscopy, or even surgical assistance, may be needed to reach the jejunojunostomy or the gastric remnant^[2,3].

LEAKS AND FISTULAS

Leaks commonly occur at the anastomosis or staple line^[2]. After RYGB, leaks are usually seen at the gastrojejunal (GJ) anastomosis, in up to 2%-5% of cases^[2,5] but can occur at any staple line or other location on the GI tract. After LSG, leaks are most common near the angle of His, where the staple line meets the gastroesophageal junction^[2,3]. This is attributed to distal stenosis, increased proximal pressure, thinner tissue, and relative vascular watershed on angiographic studies, and occurs in 1%-9% of cases^[2,4]. After duodenal switch, leaks may also be seen at the duodenojejunal (DJ) anastomosis.

Leaks are associated with significant morbidity and mortality. Although rare, with an incidence of 1%-6%, several factors are believed to contribute in their development^[2-4]. Ischemia, technical error such as overlapping staple lines, or anastomotic tension are suspected among the factors that leads to leaks^[2]. Fistulas are defined as an abnormal communication between the GI tract and another organ (in the abdomen or thorax) or surface^[7,10]. Generally, fistulas are related to acute leaks that fail to close in more than 12 weeks^[7]. Complications after RYGB are gastrogastic fistulas between the gastric pouch and remnant, fistulas to the surrounding viscous organs, or fistulas to the skin^[10].

Signs and symptoms of leaks include abdominal pain, fevers, and tachycardia^[2]. Suspicion of a leak requires thorough work up to assess the location and size of the defect, infection control with antibiotics, nutritional optimization, and appropriate therapeutic intervention^[2,4]. A CT scan is usually required to assess for intra-abdominal fluid collections. If there is any surrounding fluid collection distant to the GI lumen, this needs to be drained by interventional radiology, laparoscopically, or transluminal endoscopic debridement and

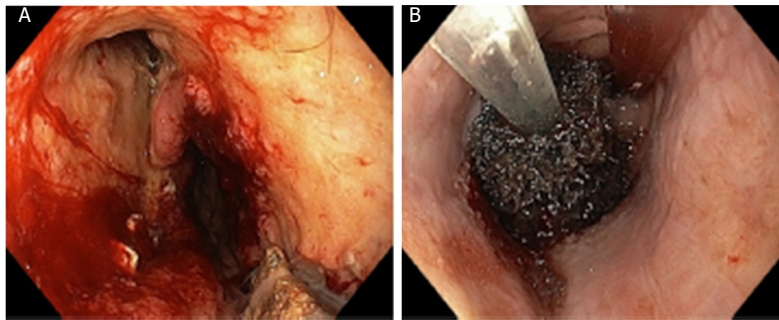


Figure 1. Leakage Endo-Sponge treatment^[6]. A: evidence of fistula; B: placement of Endo-Sponge treatment

drainage (by endo-vacuum or with pigtail catheters) [Figure 1]^[2-5,7]. Depending on the size of the fistula, different approaches can be taken. The key goals of endoscopic treatment are to cover (self-expandable metallic stents, SEMS) or close the fistula (de-epithelialization, clips, endoscopic suturing (Overstitch), and secondary intention with aid of a vacuum or septotomy)^[7]. Small fistulas can be closed with OTSC^[2,4,5]. Larger defects can be covered with stents or closed with sutures^[2,4,5,7], although surgical intervention may be required [Figure 2].

SEMS are the most commonly used endoscopic modality for leak treatment^[2-6]. The self-expandable stents are placed over the leak area, isolating the area from the esophageal and gastric secretions, preventing further contamination and enhancing healing^[2,6,7]. Patients can resume oral intake while the stent is in place, which enhances their nutrition and further healing. Stent placement is done under fluoroscopy and stents are later removed in 2-3 weeks to assess healing rate and prevent stent incorporation into the native tissue^[2-4]. Stent migration, described in > 40% of cases, is a possible complication with the usage of stents. Migration might require urgent endoscopy with stent removal and possible replacement. Modalities such as clips to minimize migration have been employed with some success. Endoscopic suturing, OTSCs, and glue injection have been used as adjuncts to stenting^[2-4]. Systematic reviews and meta-analysis have been done to show the success of stenting, with a pooled proportion of successful leak closures of 87.77%^[11].

BEZOARS

Bezoars consist of coagulated blood, undigestable fibers, undigested milk products, hair, or medications found intraluminally that do not pass through the GI tract^[2]. Bezoars can be found following bariatric surgery and may lead to bowel obstruction. The incidence of bezoar-induced obstruction is unknown since the literature consists of mostly case reports. A stricture in the GJ anastomosis or foreign bodies at the staple line can serve as a nidus for bezoar formation. Endoscopy is used for diagnosis and treatment^[2,4]. Techniques used to break the bezoar include water jet fragmentation, direct suction, and drills^[2,5,6].

FAILURE TO THRIVE

Placement of a nasogastric or nasojejunal feeding tubes can be done with endoscopy^[6]. Patients who develop complications such as fistula or leak that need to be kept *nil per os* can maintain their calorie intake through enteral feeds. Placing the tube with endoscopic guidance prevents further tissue damage^[4,6].

STRICTURE AND STENOSIS

Stricture and stenosis peaks 3-4 weeks postoperatively and presents with dysphagia to solid food that progresses to intolerance to liquids^[2,4]. Other symptoms include nausea, emesis, reflux, and epigastric pain^[7].

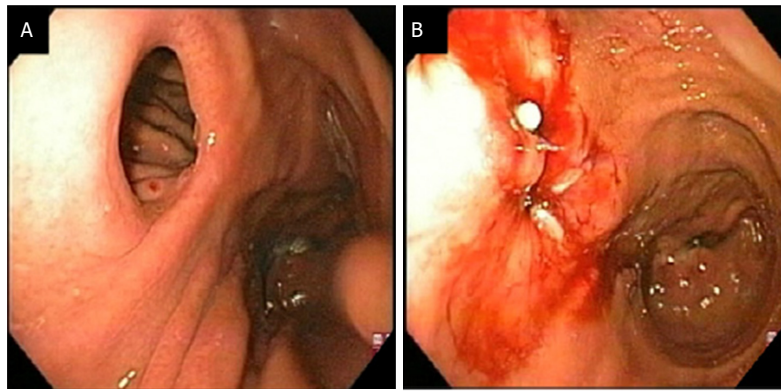


Figure 2. Gastrogastric fistula (B) after endoscopic repair^[5]. A: evidence of gastrogastric fistula; B: after endoscopic repair

After RYGB, GJ anastomotic stricture is the most common site of primary strictures^[7]. This is defined as a stoma that is < 10 mm in diameter. Stricture incidence is 3%-28%^[2,7]. Causes are multifactorial, including chemical agents [nonsteroidal anti-inflammatory drugs (NSAIDs) and tobacco], surgical technique (circular vs. linear stapler vs. hand sewn anastomosis), anastomotic tension and suture granuloma, among others^[7]. The stricture can be classified by its endoscopic appearance into mild (allowing passage of a 10.5-mm endoscope), moderate (allowing passage of an 8.5-mm pediatric endoscope), severe (allowing passage of a guidewire), or complete/near-complete obstruction (no passage of any instrumentation)^[12].

After LSG, stenosis can occur at the incisura angularis or gastroesophageal junction^[7]. Sleeve stenosis occurs in between 0.1% and 3.9% of cases^[2]. The causes are not clearly defined, but some reasons narrowing occurs are due to partial or complete over-sewing of the staple line or improper placement of the staple line (relative to the incisura or causing a torsion along its axis)^[7]. Bougie size has not been found to be a factor contributing to strictures^[7].

Treatment consists of repetitive through the scope balloon dilation or bougienage in 10-14-day intervals^[5,6] [Figure 3]. One to two dilations to 18 mm are usually enough to achieve permanent patency of the anastomosis. If the stenosis is too narrow for the scope to pass, a guidewire is used for the balloon and bougie dilation under fluoroscopy^[2,4,7]. These techniques give the endoscopist the ability to assess the resistance of the stenosis and decide if a larger balloon vs. bougie can be advanced. Strictures dilated within the first three months are more likely to be resolved with endoscopic dilation and less likely to require revisional surgery^[7]. The GJ anastomotic size should not exceed 15 mm; otherwise, the patient is at risk of weight regain^[2-6]. Resistant strictures can be managed with endoscopic stricturoplasty and/or steroid injection. For Kenalog injection, 1 mg of steroid is divided into four injections in the periphery of the stricture^[13].

A new endoscopic technique has been described for the treatment of strictures. A tunneled stricturotomy can be performed in experienced hands with good results in several case reports. Further studies are needed for long-term results^[14].

MARGINAL ULCERS

Ulceration is a late complication. Marginal ulcers are found on the jejunal side of the gastrojejunostomy in the RYGB patients^[2]. Stomal ulcers are those that occur on the gastric side of the anastomosis and are believed to be caused by local ischemia. Marginal ulcer incidence is 2%-18%^[2,4,15]. They are usually seen a few weeks or years after surgery. Risk factors for their development are poorly understood, but include poor blood supply to the anastomosis; presence of a foreign material (sutures or staples); use of NSAIDs,

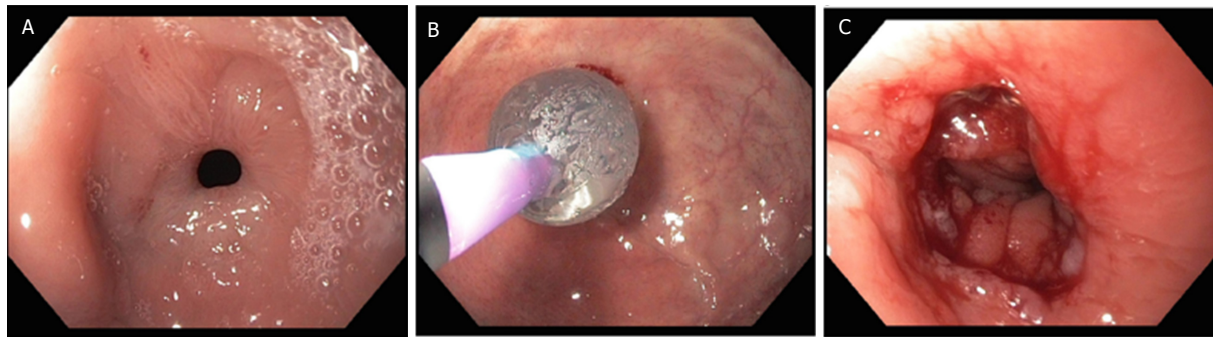


Figure 3. Anastomotic stenosis, before and after balloon dilation^[6]. A: anastomotic stenosis; B: balloon dilation; C: anastomosis after dilation

steroids, tobacco, or alcohol; chemical inflammation due to gastric secretions; and *Helicobacter pylori* infection^[2-6].

Prevention of marginal ulcers has been the focus of multiple bariatric publications. Avoiding NSAIDs, smoking cessation, and prophylactic PPIs have been the most widely used standard practices to reduce the incidence of marginal ulcers^[2,3]. Treatment includes PPIs, sucralfate solution, and misoprostol (in patients who have been taking NSAIDs)^[2,4,5,7].

EGD has been used to aid in the diagnosis and to elucidate the etiology of the ulcers. If a foreign body is identified, it should be removed to facilitate healing^[5]. These can be achieved by using over the scope grasping forceps, rat-tooth forceps, or standard endoscopic scissors^[2]. Repeat EGD should be performed to confirm healing of marginal ulcers. Non-healing or recurrent ulcers should prompt investigation of underlying problems such as gastrogastroic fistula as the cause of the ulcer^[5,6]. Ulcers that persist despite medical therapy should be considered for surgical management.

WEIGHT REGAIN

Inadequate weight loss or failure to respond to bariatric surgery is multifactorial and must be addressed with a multidisciplinary approach. Different factors have been identified: medical (anatomic factors, nutritional deficiencies, and metabolic parameters), psychological (emotional ties to cravings and food addiction), or educational (dietitian counseling, preoperative weight loss goals, calorie counting, and non-compliance to follow up)^[7].

A dilated GJ anastomosis has been associated with weight regain. This is often identified within the first two years after surgery^[7]. Multiple endoscopic techniques have been described with limited success^[2,7,16].

Endoscopic narrowing of the anastomosis can be facilitated with a variety of techniques. Some techniques, such as injection of sclerosing agents, have been abandoned due to limited success or complications^[2-4,16]. Using the OTSC or the Overstitch device are newer techniques that can be used over the scope to reduce the stoma size^[16,17]. Long-term published outcomes from these techniques are limited^[2-6,17].

BILIARY DISEASE

Cholelithiasis is frequently encountered in bariatric surgery patients, both preoperatively and postoperatively^[2]. Common bile duct stones extraction after LSG is usually achievable using a standard approach; in contrast, getting access to the papilla in patients with RYGB anatomy is difficult^[2-4]. In skillful

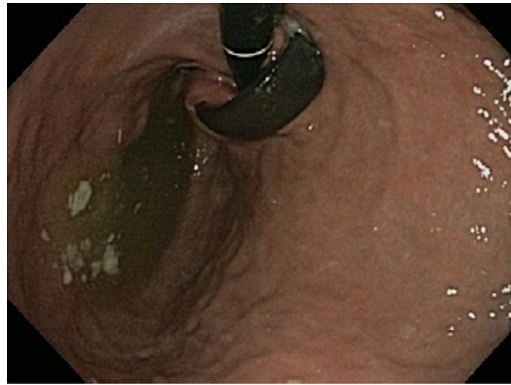


Figure 4. Band erosion^[5]

endoscopist hands, an endoscopic retrograde cholangiopancreatography (ERCP) is successful 60% of the time in these patients^[2-4]. The most common route used is to laparoscopically get access to the gastric remnant and through there get access to the papilla. An alternative is to use endoscopic ultrasound to create a gastrogastic fistula with SEMS placement, through which the scope can enable access to the papilla and subsequent ERCP^[2,6]. Closure of the resultant gastrogastic fistula following this procedure is not well studied.

BAND EROSION

Even though laparoscopic gastric banding has decreased in popularity due to its long-term complications and lack of sustained weight loss, its complications are still relatively common presentations in bariatric centers.

Transmural migration of the band through the gastric wall occurs in 7% of gastric banding patients^[2]. Endoscopy plays a role in the diagnosis and treatment of this complication. Endoscopic removal of eroded bands has been described^[2-4]. With the use of ultrasonic shears, or preferably placing a wire around the band and using an ERCP rescue device, the band and tubing complex can be cut and removed transorally^[18] [Figure 4]. Endoscopic removal is most likely to be successful if the band buckle is within the gastric lumen. Traditionally, removal of the band is performed with a combination of laparoscopy and endoscopy^[2,18].

GASTROESOPHAGEAL REFLUX DISEASE

As the rate of sleeve gastrectomy procedures performed in the US increases, the rate of *de novo* gastroesophageal reflux disease (GERD) after surgery and new-onset Barrett's esophagus has increased^[4,5]. The use of novel endoscopic techniques to address GERD after bariatric surgery has slowly gained popularity. Several case reports have been published with successful results. The use of radiofrequency energy (Stretta) is the most widely described. The antireflux mucosectomy procedure involves endoscopic mucosal resection of the gastroesophageal junction and is also described^[10,19]. The healing of the mucosal defect stimulates scar formation that improves reflux^[19]. Further studies are needed to evaluate the long-term success of this approach.

SUMMARY

As the incidence of obesity increases exponentially, so does the incidence of bariatric surgery performed in the US. Complications of these procedures can present days to years postoperatively. Many of these complications can be managed endoscopically. Advances in endoscopic techniques have facilitated a

minimally invasive approach with successful results. Upper endoscopy has been shown to be safe and cost effective in the diagnosis and treatment of bariatric surgery complications in the early and late postoperative period.

DECLARATIONS

Authors' contributions

Contributed to the design of the research, drafting of the manuscript and critical revision: Ardila-Gatas J, Pryor A

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Robotic versus open and video-assisted thoracoscopic surgery approaches for lobectomy

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Abstract

More and more data are available on the benefits of minimally invasive thoracic surgery compared to open thoracic surgery in the curative treatment of early-stage non-small cell lung cancer. However, results are conflicting, especially when video-assisted thoracoscopic surgery (VATS) is compared to robotic-assisted thoracoscopic surgery (RATS) for lobectomy. Our goal is to report the main results of recent systematic reviews and meta-analyses comparing RATS, VATS, and open surgery for lobectomy. Using PubMed database, we selected systematic reviews and meta-analyses, which compared the short-term outcomes of patients treated by RATS, VATS, or open surgery for lobectomy. In all but one of the systematic reviews, robotic lobectomy allowed similar short-term outcomes as VATS lobectomy and better short-term outcomes than open surgery. One meta-analysis by O'Sullivan *et al.* found that robotic lobectomy was associated with fewer adverse events ($P < 0.00001$) and lower 30-day mortality ($P = 0.001$), compared to VATS lobectomy. Robotic lobectomy could be a valid alternative to VATS and open lobectomy. Short-term outcomes do not appear to be different between VATS and RATS cohorts, except in one recent meta-analysis, which reported the superiority of RATS compared to VATS. Without cost analysis and randomized controlled trials with long-term outcomes, no strong conclusions can be drawn.

Keywords: Minimally invasive surgery, robotic surgery, robotic-assisted thoracoscopic surgery, video-assisted thoracoscopic surgery, lobectomy, lung cancer, short-term outcomes, review



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INTRODUCTION

Surgery is the cornerstone of early stage non-small cell lung cancer (NSCLC) treatment, and lobectomy is currently the preferred type of lung resection for clinical stages I and II of NSCLC^[1]. Minimally invasive approaches, namely video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS), are preferred for early stage NSCLC, and are even recommended for those early stage NSCLC^[2]. Robotic thoracic surgery has developed rapidly since the first publication by Melfi *et al.*^[3] in 2002, which reported the first cases of robotic thoracic procedures including five lobectomies.

Thoracic surgery approaches have evolved during the last two decades, as has the way of performing lung lobectomy, but not its goal. Lobectomy for NSCLC involves two steps, namely lung resection and complete lymph node resection, according to international recommendations^[1,4-12]. Minimally invasive surgery provides better short-term outcomes compared to open surgery, with fewer adverse events and shorter length of hospital stay^[13-15]. Until recently, many systematic reviews with meta-analyses and large retrospective databases comparing VATS and RATS lobectomy have provided conflicting results regarding short-term outcomes.

Our goal in this mini-review is to report the main results of recent systematic reviews and meta-analyses comparing the short-term outcomes of patients treated by RATS, VATS, or open surgery for lobectomy.

METHODS

PubMed and Web of Science were searched to identify potentially eligible literature up to 1 October 2019 reporting lobectomy performed by open surgery, VATS, or RATS and to collect data on the short-term outcomes of patients according to each surgical approach. The search items were: “video-assisted thoracoscopic surgery” OR “VATS”, “robotic-assisted thoracoscopic surgery” OR “RATS”, “thoracotomy”, “lobectomy”, “lung cancer”, “techniques”, “systematic review” AND “meta-analysis”, AND “national database”. Only articles in English language were included.

RESULTS

Performing lobectomy: common points and differences between RATS, VATS, and open thoracotomy

With the advent and the spread of minimally invasive surgery, such as VATS and RATS, the use of open thoracotomy as the “gold standard approach” has decreased. Thoracotomy includes two approaches: anterolateral thoracotomy and posterolateral thoracotomy. With both approaches, whenever possible, a muscle sparing incision is made. To perform lobectomy for NSCLC, a hilar dissection or a fissureless technique is used. Mediastinal lymph node dissection is done before or after lobectomy. Thoracotomy is still the main approach to perform lobectomy for early stage NSCLC: between 2010 and 2012, 67% of lobectomies were performed by open thoracotomy, 26% by VATS, and 7% by RATS, as registered in the USA nationwide cancer database^[16].

VATS for early stage NSCLC is now well accepted, with better short-term outcomes^[17,18] [Table 1]. With VATS, a fissureless technique is preferred and mediastinal lymph node dissection is done at the end of the procedure. Despite the benefits associated with VATS lobectomy, this approach is not universally used for many reasons. The main reason is the technical difficulty in performing complete hilar, lobar, interlobar, and mediastinal lymph node resection^[19] according to international recommendations.

RATS offers some advantages compared to VATS. First, structures are magnified with a stable, high-quality 3D optical instrument directed by the surgeon and not by the surgeon's assistant. Instruments have up to seven degrees of freedom due to the Endowrist system. With RATS, lobectomy adheres to oncologic

Table 1. Main reports concerning short-term outcomes after lobectomy performed by thoracotomy or a minimally invasive approach as VATS or RATS for a NSCLC in studies used for this article

Ref.	Population study	Outcomes	Results
Ng et al. ^[13]	Comparison of multiport and uniport VATS and RATS 145 studies, 369,793 patients Comparison of VATS to Open: 115 studies	VATS vs. Open Nodal upstaging Complications 90-day mortality Length of hospital stay 5-year OS 5-year DFS VATS vs. RATS Nodal upstaging Complications 30-day mortality Length of hospital stay 5-year OS 5-year DFS	OR 0.71 (95%CI 0.58-0.87) $P < 0.001$ OR 0.64 (95%CI 0.59-0.71) $P < 0.001$ OR 0.78 (95%CI 0.56-1.07) $P = 0.12$ -1.9 d (95%CI -2.25 to -1.54) $P < 0.001$ OR 1.35 (95%CI 1.17-1.56) $P < 0.0001$ OR 1.15 (95%CI 0.94-1.4) $P = 0.18$ OR 1.02 (95%CI 0.85-1.22) $P = 0.87$ OR 1.28 (95%CI 0.75-2.17) $P = 0.37$ OR 1.04 (95%CI 0.73-1.47) $P = 0.85$ -0.16 d (95%CI -0.81 to -0.48) $P = 0.62$ OR 0.79 (95%CI 0.47-1.33) $P = 0.38$ OR 0.71 (95%CI 0.44-1.14) $P = 0.16$
O'Sullivan et al. ^[14]	Comparison of short-term outcomes after lobectomy performed by Open, VATS or RATS 112,356 patients	RATS vs. Open Complications 30-day mortality Length of hospital stay Operative time RATS vs. VATS 30-day mortality Operative time	OR 0.67 (95%CI 0.58-0.76) $P < 0.00001$ 0.53 (95%CI 0.33-0.85) $P = 0.08$ WMD -1.4 (95%CI -1.96 to -0.85) $P < 0.00001$ WMD 65.56 (95%CI 53.66-77.46) $P < 0.00001$ OR 0.61 (95%CI 0.45-0.83) $P = 0.001$ WMD 4.98 (95%CI 2.61-7.36) $P < 0.001$
Adams et al. ^[29]	Comparison of short-term outcomes after a lobectomy RATS to VATS and Open in a national Database $n = 116$ RATS $n = 4612$ VATS $n = 5913$ Open	RATS vs. Open Operative time Postoperative blood transfusion Air leak > 5 days Chest tube duration Length of hospital stay 30-day mortality RATS vs. VATS Operative time Postoperative blood transfusion Air leak > 5 days Chest tube duration Length of hospital stay 30-day mortality	241 min vs. 175 min, $P < 0.001$ 0.9% vs. 7.8%, $P = 0.002$ in % of patient 5.2% vs. 10.8%, $P = 0.05$ 3.2 days vs. 4.8 days, $P < 0.001$ 4.7 days vs. 7.3 days, $P < 0.001$ in median 0% vs. 2.2%, $P = 0.18$ 241 min vs. 179 min, $P < 0.001$ 0.9% vs. 3.8%, $P = 0.13$ in % of patient 5.2% vs. 8.9%, $P = 0.17$ 3.2 days vs. 3.7 days, $P = 0.18$ 4.7 days vs. 5.3 days, $P = 0.07$ 0% vs. 1%, $P = 0.63$
Agzarian et al. ^[30]	Comparison of short-term outcomes after a lobectomy RATS to VATS and Open 20 articles	RATS vs. Open Operative time Length of hospital stay RATS vs. VATS Operative time Length of hospital stay	WMD 40.10 (95%CI -50.76 to -130.96) $P = 0.39$ -1.97 days (95%CI -4.05 to -0.1) $P = 0.06$ in median WMD 64.28 (95%CI -50.35 to -178.91) $P = 0.27$ -0.68 days (95%CI -1.52 to -0.16) $P = 0.11$
Kent et al. ^[15]	Comparison of short-term outcomes after a lobectomy RATS to VATS and Open in a national database $n = 411$ RATS $n = 1233$ VATS $n = 1233$ Open for propensity-matched analysis	RATS vs. Open Complication rate Mortality rate Length of hospital stay RATS vs. VATS Complication rate Mortality Length of stay	43.8% vs. 54.1%, $P = 0.003$ 0.2% vs. 2%, $P = 0.016$ 5.9 days vs. 8.2 days, $P < 0.0001$ in median 43.8% vs. 45.3%, $P = 0.674$ 0.2% vs. 1.1%, $P = 0.122$ 5.9 days vs. 6.3 days, $P = 0.454$
Rajaram et al. ^[31]	Comparison of short-term outcomes after a lobectomy RATS to VATS and Open in a national database $n = 3238$ to 3689 RATS $n = 3401$ to 3689 VATS $n = 3405$ to 3689 Open for propensity-matched analysis	RATS vs. Open Length of hospital stay 90-day Mortality 30-day unplanned readmission RATS vs. VATS Length of hospital stay 90-day Mortality 30-day unplanned readmission	6.1 days vs. 5.7 days, $P < 0.001$ in median 3% vs. 3.4%, $P = 0.097$ 4.1% vs. 4%, $P = 0.81$ 6.1 days vs. 5.9 days, $P = 0.019$ in median 3% vs. 2.8%, $P = 0.877$ 4.1% vs. 4.6%, $P = 0.258$
Cao et al. ^[32]	Comparison of short and long term outcomes after a lobectomy RATS and VATS $n = 941$ patients For meta-analysis for short-term outcomes $n = 160$ RATS and $n = 372$ Open	RATS vs. Open Complication rate Length of hospital stay	RR 0.77 (95%CI 0.54-1.09) $P = 0.14$ Shorter in RATS group $P < 0.05$

Paul <i>et al.</i> ^[33]	Comparison of short-term outcomes after a lobectomy RATS and VATS in a sample of a nationwide database <i>n</i> = 2498 RATS <i>n</i> = 37,595 VATS	RATS <i>vs.</i> VATS Length of hospital stay Complication rate In-Hospital mortality Total Costs	5 days <i>vs.</i> 5 days, <i>P</i> = 0.23 in median 50.1% <i>vs.</i> 45.2%, <i>P</i> = 0.32 0.7% <i>vs.</i> 1.3%, <i>P</i> = 0.15 22.582\$ <i>vs.</i> 17.874\$ <i>P</i> < 0.001 (Median)
Emmert <i>et al.</i> ^[35]	Comparison of short-term outcomes after a lobectomy RATS and VATS <i>n</i> = 3758 RATS <i>n</i> = 58,677 VATS	RATS <i>vs.</i> VATS Length of hospital stay Operative time Chest tube duration Mortality	-1.08 days (95%CI -2.33 to -0.17) <i>P</i> = 0.078 mean difference 8.97 min (95%CI -28.12 to -46.07) <i>P</i> = 0.56 mean difference -0.71 days (95%CI -1.5 to -0.1) <i>P</i> = 0.064 mean difference OR 0.52 (95%CI 0.29-0.93)
Louie <i>et al.</i> ^[34]	Comparison of short term outcomes after a lobectomy RATS and VATS <i>n</i> = 1220 RATS <i>n</i> = 12,378 VATS National Database	RATS <i>vs.</i> VATS Operative time Air Leak > 5 days Length of hospital stay < 4 days 30-day mortality	186 min <i>vs.</i> 173 min <i>P</i> < 0.001 10% <i>vs.</i> 9.8% <i>P</i> = 0.8135 48% <i>vs.</i> 39% <i>P</i> < 0.001 0.6% <i>vs.</i> 0.8% <i>P</i> = 0.4
Wei <i>et al.</i> ^[36]	Comparison of short-term outcomes after a lobectomy RATS and VATS <i>n</i> = 4727 RATS <i>n</i> = 56,232 VATS before matched analysis	RATS <i>vs.</i> VATS for matched cohort 30-day mortality Postoperative morbidity	RR 0.12 (95%CI 0.01-1.07) <i>P</i> = 0.06 RR 0.95 (95%CI 0.83-1.08) <i>P</i> = 0.41

DFS: disease free survival; HR: hazard ratio; OS: overall survival; OR: odds ratio; RATS: robotic-assisted thoracic surgery; RR: risk ratio; VATS: video-assisted thoracic surgery; WMD: weighted mean difference; NSCLC: non-small cell lung cancer

principles as anatomical dissection and allows better lymph node dissection^[20,21]. The main limitations for the wide deployment of RATS are the higher cost of the procedure compared to VATS^[22] and logistical issues.

Lymph node dissection and nodal upstaging by RATS, VATS, and open thoracotomy

Intraoperative lymph node assessment is a critical component in the surgical treatment of NSCLC. Since the development of VATS, there has been controversy concerning lymph node dissection performed by VATS compared to open surgery. Studies have described the feasibility of using VATS to perform complete lymph node dissection and even nodal upstaging, although less commonly than by open surgery. With its intrinsic features, lymph node dissection has been described as easier to perform by RATS than by VATS^[21,23].

Kneuert *et al.*^[24] recently published a propensity-score adjusted comparison of lymph node upstaging by RATS, VATS, and open surgery during lobectomy for a cN0/N1 NSCLC in two centers. Between 2011 and 2018, 911 patients were included (254 RATS, 296 VATS, and 261 open surgery). The overall rate of lymph node upstaging was highest with open lobectomy (21.8%), followed by RATS (16.2%) and VATS (12.3%) (*P* = 0.03), with no difference concerning mediastinal N2 upstaging (*P* = 0.6). More nodes were sampled by open surgery (4) than by RATS (3.8) and VATS (3.6) (*P* = 0.001). Finally, on multivariate analysis, the rate of lymph node upstaging was lower for VATS compared to open surgery (OR 0.5, 95%CI 0.29-0.85, *P* = 0.01) and not different between RATS and open surgery (OR 0.72, 95%CI 0.44-1.18, *P* = 0.19). Multiple contemporary studies have reported the same overall long-term survival between VATS lobectomy and open lobectomy, which suggests that there is no decreased long-term survival for patients treated by VATS^[25,26]. Medbery *et al.*^[27] reported a lower rate of nodal upstaging with VATS than with open surgery (*P* < 0.001), but, in the subgroup of patients operated on in a university hospital, there was no difference between groups (*P* = 0.08). Recently, Yang *et al.*^[28] reported an absence of difference in the rate of nodal upstaging of patients with clinical T1-T2 N1 MO NSCLC and performed by VATS or open surgery (12% and 10.5%, respectively, *P* = 0.41). The five-year overall survival was not different between the two groups (48.6% and 48.7%, respectively, *P* = 0.76). With RATS, the rate of nodal upstaging was not different compared to open surgery, and higher than with VATS^[20,21].

Main results of meta-analysis and systematic reviews according to lobectomy performed by RATS, VATS, or open surgery

Ng *et al.*^[13] published the latest and most extensive systematic review and meta-analysis in 2019 comparing VATS to open thoracotomy, VATS to RATS, and also multiport and uniport VATS. They included 138 studies and 7 randomized controlled trials with 369,793 patients. They analyzed short-term outcomes such as complications, mortality, and oncologic quality criteria with lymph node dissection and long-term outcomes. They also analyzed functional data with pain, quality of life, pulmonary function, and cost-effectiveness. They reported a lower complication rate with VATS lobectomy than with open lobectomy (OR 0.64, 95%CI 0.59-0.71, $P < 0.001$), and no difference in mortality rate (OR 0.78, 95%CI 0.56-1.07, $P = 0.12$). The rate of nodal upstaging was lower with VATS than with open surgery (OR 0.71, 95%CI 0.58-0.87), with no difference in the number of lymph nodes resected ($P = 0.18$) or nodal stations explored ($P = 0.49$). They found no difference in the rate of nodal upstaging between VATS and RATS (OR 1.02, 95%CI 0.85-1.22, $P = 0.87$). Length of hospital stay was shorter after VATS than open surgery, -1.9 days (95%CI -2.25 to 1.54, $P < 0.001$), but there was no difference between VATS and RATS, -0.16 days (95%CI 0.81-0.48, $P = 0.62$). Concerning long-term outcomes, five-year overall survival was improved after VATS lobectomy compared to open lobectomy (OR 1.35, 95%CI 1.17-1.56, $P < 0.0001$), with no difference observed in disease free survival (OR 1.15, 95%CI 0.94-1.40, $P = 0.18$). There was no difference in five-year overall survival between VATS and RATS (OR 0.79, 95%CI 0.47-1.33, $P = 0.38$) or in five-year disease free survival (OR 0.71, 95%CI 0.44-1.14, $P = 0.16$). The main results of the reports analyzed in this article are presented in [Table 1](#).

O'Sullivan *et al.*^[14] published in 2018 the first systematic review and meta-analysis and concluded that RATS lobectomy significantly improved the short-term outcomes of patients more than VATS or open lobectomy. After RATS lobectomy, compared to open lobectomy, there was an improvement in short-term outcomes, with fewer complications (OR 0.67, 95%CI 0.58-0.76, $P < 0.00001$), lower 30-day mortality (OR 0.53, 95%CI 0.33-0.85, $P = 0.08$), and shorter length of hospital stay with weighted mean difference (WMD) of -1.4 days (95%CI -1.96 to 0.85, $P < 0.00001$), but longer operative times with WMD of 65.56 min (95%CI 53.66-77.46, $P < 0.00001$). After RATS lobectomy, compared to VATS lobectomy, there was a lower rate of 30-day mortality (OR 0.61, 95%CI 0.45-0.83, $P = 0.001$), with longer operative times with WMD of 4.98 min (95%CI 2.61-7.36, $P < 0.001$).

Adams *et al.*^[29] in 2014 published one of the first retrospective multicenter comparisons of short-term outcomes after lobectomy performed by RATS, VATS, or open surgery and concluded that RATS was equivalent to VATS for all intraoperative and postoperative outcomes, but allowed better short-term outcomes compared to open surgery. Their main results were lower rates of postoperative blood transfusion (0.9% *vs.* 7.8%, $P = 0.002$), fewer air leaks of more than five days (5.2% *vs.* 10.8%, $P = 0.05$), shorter duration of chest tube placement (3.2 days *vs.* 4.8 days, $P < 0.001$), and shorter length of stay (4.7 days *vs.* 7.3 days, $P < 0.001$). Agzarian *et al.*^[30], Kent *et al.*^[15], and Rajaram *et al.*^[31] concluded that RATS was not superior to VATS for perioperative outcomes. Compared to open surgery, RATS was found superior with fewer perioperative outcomes^[32].

Until the publication of O'Sullivan *et al.*^[14], systematic reviews and meta-analyses^[32-36] found small significant differences in short-term outcomes between RATS and VATS lobectomy or no difference between these two minimally invasive surgical approaches.

Minimally invasive approaches for locally advanced NSCLC

Petersen *et al.*^[37] in 2006 were among the first to demonstrate that VATS lobectomy was safe and feasible for selected patients with NSCLC who had received induction chemotherapy or chemoradiotherapy. They reported short-term outcomes with no increase in the number of adverse events after VATS resection and with the same oncologic efficacy. Yang *et al.*^[38] reported a propensity score matched analysis, in which survival of patients operated by VATS after induction chemotherapy with or without radiotherapy was

similar to those who were operated by an open approach ($P = 0.56$). Moreover, 30-day mortality was similar ($P = 0.69$). Veronesi *et al.*^[39] reported a multicenter retrospective cohort of patients with stage III NSCLC and operated by a RATS procedure in seven high volume centers. They reported 223 NSCLC, 32% of which were diagnosed cN2 preoperatively and 68% intraoperatively. The rate of conversion to thoracotomy was 9.9%, and the rate of Grade 3 and more complications was 10.3%. For patients who received neoadjuvant chemotherapy, the rate of conversion to thoracotomy was 15%, the rate of Grade 3 and 4 complications was 12%, and all were resected with R0 margins. Overall 90-day mortality was 4% but no patient who received neoadjuvant chemotherapy died. Three-year overall survival was 61.2%, while 60.3% in the group of patients treated by neoadjuvant chemotherapy ($P = 0.6$).

DISCUSSION

In this mini-review, we compare short-term outcomes between lobectomy performed by minimally invasive VATS and RATS and lobectomy by open surgery. For several decades, VATS lobectomy has allowed better short-term outcomes compared to open surgery with at least the same long-term oncologic outcomes. These results were obtained by systematic review and meta-analysis of retrospective series and of some randomized controlled trials.

Before discussing the reported results, the common points and differences among RATS, VATS, and open approaches are clarified. Together, there are three surgical approaches but two surgical feelings and two resection concepts for lung lobectomy.

Regarding surgical feelings, also called haptic - force and tactile - feedback, compared to open surgery, VATS allows us to feel each tension exerted on the tissues, because we directly manipulate the tissue, lung, lymph nodes, and other structures. Conversely, the robotic platform is a robotic device guided by the surgeon using a digital interface. With the Da Vinci platform, we do not receive sensitive feedback in our hands. This lack of feedback is one of the criticisms made of this surgical tool. However, “when one feeling is lacking, we say that another develops”. Thus, surgeons who can no longer rely on touch see their eyes sharpen, becoming an extension of their hands. With training, they learn and feel the tension exerted on the tissue by seeing the latter exerted on the tissue, allowing them to exceed this limit. The surgeon assistants who expose and retract the lung will also help the operator surgeons, because they can feel the exerted tension on lung by the robot and thus the operator. Nevertheless, robotic surgery industries are studying haptic feedback, but each robotic system is different, thus each research system is different. Moreover, it is important to first understand how we perceive force and tactile information, because it will affect the way we design haptic displays^[40].

Regarding resection concepts, compared to VATS and the anterior approach - e.g., fissureless technique - RATS allows us to mimic open surgery techniques. The robotic platform allows thoracic surgeons to perform a lobectomy, as they would have done using an open approach. Conversely, the fissureless approach in VATS lobectomy is a necessary adaptation of a surgical technique.

In 2016, Bendixen *et al.*^[18] published a randomized controlled trial comparing lobectomy by VATS and by anterior muscle sparing thoracotomy. For VATS, the authors observed less pain on Postoperative Day 1 ($P = 0.0012$) and during the year after resection ($P < 0.0001$), as well as better quality of life according to EuroQol 5 Dimensions (EQ5D) ($P = 0.014$). Nevertheless, they found no difference between VATS and thoracotomy for postoperative Grade 3 and 4 adverse events, and quality of life according to the European Organisation for Research and Treatment of Cancer 30-item quality of life questionnaire (QLC-C30) ($P = 0.13$). More recently, the first results of the randomized controlled VIOLET study^[41] confirmed better short-term outcomes after lobectomy by VATS than by open surgery.

Postoperative complications affect mortality, and major one, as Grades ≥ 3 according to the Clavien-Dindo classification, have a significant impact on mortality but are rare, with a rate of 4.3% in the multicenter and retrospective review published by Cao *et al.*^[42]. This rate was comparable to outcomes of the CALGB 39802 study, which reported a rate of 7.4% for Grade ≥ 3 postoperative complications after a VATS lobectomy^[43]. In robotic practice, better short-term outcomes were observed after lobectomy by RATS than by open thoracotomy. However, most meta-analyses reported the same short-term outcomes, with as negative points longer operative times and more costly procedures compared to VATS lobectomy^[13,15,29-31,34-36,44]. Only O'Sullivan *et al.*^[14] reported better short-term outcomes with fewer adverse events after lobectomy by RATS compared to VATS in a systematic review with meta-analysis. Nevertheless, some authors reported in retrospective studies a clear benefit of RATS compared to VATS. Reddy *et al.*^[45] recently reported a propensity-matched comparison of lobectomies by surgeons who performed 20 or more VATS or RATS procedures annually. With 838 patients in each group, they observed in the RATS group a lower rate of conversion (4.8% vs. 8%, $P = 0.007$), a lower rate of 30-day complications (33.4% vs. 39.2%, $P = 0.0128$), and no difference in mortality rate, but with longer operative times by 25 min ($P < 0.0001$). They concluded in favor of RATS lobectomy for surgeons performing more than 20 procedures annually. One complication that is less often reported after robotic lobectomy is postoperative anemia requiring blood transfusion. Indeed, robotic surgery allows performing very precise gestures and in particular elective hemostasis during hilar dissection and lymph node resection. For example, Adams *et al.*^[29] reported fewer blood transfusion after a RATS lobectomy compared to a VATS or open lobectomy ($P < 0.05$).

Cost is presented as one of the major drawbacks of RATS^[22]. In the current context of resource management, Gondé *et al.*^[46] conducted a precise assessment of the economic impact of RATS surgical innovation compared to VATS. RATS lobectomy was found more expensive than VATS lobectomy, and median total costs were €10,972 vs. €9637 ($P = 0.007$). Costs related to length of stay were not different ($P = 0.061$), but excessive costs reported in the RATS group were explained by expensive medical devices and supplies used for RATS lung resection ($P = 0.004$). Nevertheless, these authors reported a significantly lower cost of their minimally invasive techniques compared to the mean cost in France ($P = 0.001$). Conversely, VATS was found to be a cost-effective alternative compared to thoracotomy in the randomized controlled trial of Bendixen *et al.*^[47], with a savings of €4267 ($P < 0.001$). Subramanian *et al.*^[48] reported that, compared to open lobectomy, RATS lobectomy was 13% more expensive ($P < 0.001$) and VATS lobectomy 2% less expensive ($P = 0.007$). In their report, they analyzed operating room costs and in-hospital costs from patients operated between 2008 and 2014 in Florida, with data from the Healthcare Cost and Utilization Project Florida State Inpatient Database. Minimal approaches were also associated with improved clinical outcomes compared to open lobectomy ($P = 0.016$), and increased operating room costs were compensated by in-hospital savings. Recently, Kneuert *et al.*^[49] reported a cost analysis performed at their center. They analyzed data from 697 patients operated by RATS ($n = 296$), VATS ($n = 161$), and open ($n = 240$) for a lobectomy between 2012 and 2017 and performed a propensity score adjustment. Unlike our report^[46], and that of Subramanian *et al.*^[48], the overall cost - including operating room costs and in-hospital costs - of the three approaches were similar: RATS \$17,223, VATS \$17,260, and open \$18,075 ($P = 0.48$). Nevertheless, RATS and VATS approaches were associated with higher operating room costs - RATS \$9912 and VATS \$9491 - compared to open thoracotomy - \$8698 ($P = 0.001$). Finally, according to their experience, despite the higher operating room costs calculated for RATS and VATS, it was recovered by postoperative costs reductions associated with improved postoperative outcomes and shorter hospital stay ($P < 0.001$). These three articles^[46,48,49] reported higher operating room costs for RATS lobectomy but compensated by improved outcomes compared to thoracotomy. Nevertheless, RATS will always be more expensive, and our goal is to reduce this economic gap. Because patients are well prepared and conditioned within the framework of enhanced recovery protocols, they allow better short-term outcomes for patients operated by thoracotomy and lead to fewer adverse events, shorter length of hospital stay, and logically cost reductions for these patients in 2020 compared to patients operated 5 or 10 years ago.

Minimally invasive lobectomy performed by VATS or RATS is recommended for early stage NSCLC^[1] and the majority of series in this mini-review included stage I NSCLC. Some authors advocate the effectiveness of VATS and RATS for loco-regionally advanced NSCLC. More and more studies have described the effectiveness of a VATS approach for N positive status^[50] and combined resection of a lobe, e.g., with the chest wall^[51], the superior vena cava^[52] or a sleeve resection^[53]. For stage IIIA NSCLC, a VATS approach allowed at least the same long-term outcomes compared to thoracotomy, but with better short-term outcomes^[38]. Extended indications for loco-regionally advanced NSCLC are being explored in robotic thoracic surgery. With the benefits of improved visualization, stability, dexterity, and accuracy, some technical aspects of lobectomy, with complete lymph node dissection, are described as easier to perform by RATS than by VATS^[23,54-56], with no difference in long-term outcomes.

Performing minimally invasive surgery using a digital interface has enabled the use of innovative techniques and concepts. The first concept is the use of the simulation tool in the technical learning process. Thus, before performing their first minimally invasive lung resection on a patient, trainee surgeons are able to train on high definition digital simulators close to the reality of the operating room and thus improve their technical skills^[57,58]. Moreover, with a high-definition CT scanner and 3D modeling, it is possible to precisely plan a complex lung resection such as a segmentectomy on 3D representation^[59]. In addition, 3D modeling can be visualized on screen. This augmented reality can be used for liver surgery, for example, but still requires development for lung resection. 3D augmented reality could be used for VATS and RATS surgery and even for open surgery, by using specific glasses. The second concept is the use of safety controls via the robotic platform. Thus, before starting a procedure, security elements are specified to unlock the robot or even the optics of the VATS column to prevent intraoperative accidents.

The majority of the included studies did not use propensity matching, but included heterogeneous groups of patients in terms of disease stage, comorbidity, and surgical approaches. This heterogeneity could potentially mask some results, but reflects “real-life practices in our unit”. As such, this mini-review does not provide conclusive evidence regarding the superiority of RATS compared to VATS for short-term outcomes. A randomized controlled trial is required to provide conclusive answers.

CONCLUSION

Robotic lobectomy could be a valid alternative to open surgery, and provides at least the same short-term outcomes compared to VATS. Based on the findings of recent meta-analyses, lobectomy performed by RATS compared to VATS could allow lower 30-day morbidity and mortality, but with longer operative times and higher surgical costs. According to recent reports, robotic technology seems to be a reasonable alternative to VATS and open surgery. This result must be interpreted with caution, as we cannot exclude an inherent bias related to meta-analyses. A randomized controlled trial with cost analysis and long-term follow-up may be useful to understand the role of robotic technology in thoracic surgery for the benefit of patients with NSCLC.

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Authors' contribution

Collected and selected articles: Montagne F, Baste JM

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Original Article

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Computed tomography-3D-volumetry: a valuable adjunctive diagnostic tool after bariatric surgery

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Abstract

Aim: After bariatric surgery, a variety of complaints may arise. Identification of the causes of such symptoms is often challenging due to the postoperatively modified anatomy. While standard examinations with upper endoscopy and upper gastrointestinal series might miss the three-dimensional anatomic nature of the problem, quantitative three-dimensional computed tomography volumetry (3D-CT) of the upper gastrointestinal tract offers a novel, adjunctive examination, revealing the detailed anatomy. The aim of this study was to analyse the clinical value of 3D-CT in post-bariatric patients.

Methods: Prospective data of 279 patients, who underwent 3D-CT due to complications after different bariatric procedures, were retrospectively analysed. Directly before examination, the surgical-modified stomach was distended with an effervescent-powder. CT images were 3D-reconstructed and, further, gastric volume was calculated.

Results: In total, 279 patients were examined. Time between surgery and examination was significantly different between Roux-en-Y gastric bypass ($n = 168$) (54.3 ± 38.6 months) and sleeve gastrectomy ($n = 78$) (27.8 ± 21.7 months) ($P = 0.0001$). Others, less numerous, but included procedures were one-anastomosis/mini gastric bypass ($n = 11$), and dated procedures, such as the vertical banded gastrostomy. The examination allowed calculation of the gastric volume, and the 3D-reconstructions depicted accurately the pivotable anatomic details of the modified upper gastrointestinal tract with 360° view. As a robust result, patients with a higher gastric volume showed more weight regain after sleeve gastrectomy.



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Conclusion: 3D-CT is easy-to-perform and facilitates identification of the post-surgical three-dimensional gastric anatomy. It represents a valuable additional diagnostic tool in post-bariatric patients with post-procedural complications. 3D-CT might be an important preoperative tool prior to revisional surgery. In addition, this is the only exact and reproducible calculation of the gastric volume.

Keywords: Gastrointestinal tract, computed tomography, gastric volumetry, 3D-reconstruction, anatomical accuracy

INTRODUCTION

Bariatric surgery has been shown to be an effective and safe treatment for obesity and metabolic disorders^[1-3]. However, a number of postsurgical complications may arise, including gastroesophageal reflux disease (GERD), epigastric pain, vomiting, and, especially in bariatric patients, poor weight loss or weight regain^[4,5]. These symptoms can appear at different times. Some are evident already shortly after the operation, but others appear only years after a procedure. Whilst weight regain is such a special issue in bariatric patients, an objective measurement of gastric or pouch volume is difficult, even if the increase in gastric volume is being discussed more and more as an underlying cause. Comparability of former, contemporary and future examinations is even more complex. Upper endoscopy (UE) and upper gastrointestinal series (UGI) are the most important diagnostic tools after general surgery of the upper gastrointestinal tract. While the sensitivity of UE is high in patients with upper gastrointestinal symptoms^[6], in the case of insufficient weight loss or weight regain, as well as in anatomically confusing conditions, UE and UGI contrast studies are often not conclusive. UE is more useful in gathering information concerning pouch- or stoma-related complications, whereas UGI is a more effective means of detecting oesophageal or Roux-limb abnormalities^[7], all of which are possible standard reasons for upper abdominal pain after bariatric surgery, but mostly do not account for an occurring weight regain or, moreover, the special complications that have already tried to be clarified before and elsewhere.

Quantitative three-dimensional computed tomography volumetry (3D-CT) of the upper gastrointestinal tract is a not very widespread technique and is rarely used in general, but for years has been frequently used in some specialised bariatric centres. By providing pivotable, 3D-reconstructed pictures of the anatomy, on the one hand, it enables robust and accurate preoperative planning in patients undergoing complex revisional bariatric surgery^[8]. On the other hand, and as a worthwhile side-effect of the technique itself, 3D-CT is a useful and exclusive tool for accurate volume measurement. For example, with the aid of 3D-CT, Hanssen *et al.*^[9] demonstrated that initial sleeve volume ≥ 100 mL is significantly related to insufficient weight loss after bariatric surgery.

The aim of this study was to demonstrate the clinical usefulness of 3D-CT to assess accurately the shape and anatomy, and, further, its additional value as an exclusive diagnostic tool for gastric volumetry and quantitation after bariatric surgery.

METHODS

Examination protocol of the 3D-CT

To achieve a high level of comparability, a standardised examination protocol for the 3D-CT was invented and established years ago. A dedicated and trained bariatric team monitored all examinations.

Patients had to fast at least 6 h before the scheduled examination. To prepare for the CT-study, shortly before the examination, all patients received 20 mg butylscopolamin as intravenous injection to reduce gastrointestinal motility during the procedure. Immediately before scanning, each patient swallowed 11.8 g (two sachets) of a commercially available effervescent powder (Ahoi Brause, Frigeo), which is normally used in the preparation

of an aromatised, acidulous sherbet or just as sour candy. A contrast itself is not necessary for the examination. Patients were already sitting on the CT-table during the intake. The effervescent powder creates an instant froth, thus causing immediate distention of the stomach and its adjacent anatomical structures during examination. In addition, the patients were instructed to keep the froth strictly within the stomach and therefore avoid belching. Another reason for insufficient distention can be a prolonged time span between intake and examination. Thus, immediately after intake, the patient lies back to a supine examination position. Directly afterwards, the images are acquired using a Philips Brilliance 64-slice CT-scanner. The scan itself is recorded with a collimation of 32 mm \times 1.25 mm. This defines the table traverse speed during one gantry rotation of 32 mm, thus capturing a 1.25 mm layer. The corresponding pitch factor is 0.906. After the examination, the 3D-reconstruction is calculated with the Philips workstation and the IntelliSpace Portal. The resulting 3D-pictures are 360° rotatable, and accurately display the stomach and its adjacent gastrointestinal structures, here integrated in the patient's semi lucent skeleton.

Statistics

During 24 months, 279 patients underwent the 3D-CT at Sana Klinikum Offenbach, a high-volume certified centre of excellence for obesity and metabolic surgery by the European Accreditation Council for Bariatric Surgery, as part of our standard diagnostic algorithm for patients after bariatric surgery with remaining unclear symptoms after standard diagnostic examinations (UE and UGI). Patients with various bariatric procedures were included [sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), one-anastomosis/mini gastric bypass (OAGB/MGB), gastric banding (GB), vertical banded gastrostomy (VBG) and biliopancreatic diversion (BPD)], which led to the definition of three main subgroups (Bypass, SG and others). Examination data were collected prospectively and evaluated retrospectively.

Demographic and clinical data include gender, age, height in cm, weight in kg, BMI in kg/m² prior to surgery and prior to the examination and excess weight loss (EWL) in assuming ideal body weight to be that equivalent to a BMI of 25 kg/m². Time between surgery and examination was considered. Statistical analysis was performed using SPSS 11.0 statistical software for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Continuous variables, when normally distributed, were reported as mean, standard deviation (SD) and range. Intergroup differences were tested by a two-sample *t* test for normally distributed data. A *P*-value < 0.05 was considered significant.

The study was conducted in accordance with the principles of the Declaration of Helsinki. This analysis represents a partial result of a study, evaluating postsurgical endoscopies within this period, which was reviewed and approved by the ethics committee of the regional regulatory institution, Landesärztekammer Hessen (FF 111/2016; ClinicalTrials.gov Identifier: NCT03532646). Additionally, all participants provided written informed consent for data sharing.

RESULTS

Descriptive statistics

General patient data

This study included 279 post-bariatric patients [Table 1], of whom 223 were females (79.9%). Only some of the patients came from the centre's primary collection. Nearly 37% (103/279, 36.91%) were referred from other national or international bariatric centres, with the treatment mandate to solve complications that were previously intractable.

Significantly more than half of the patients (183/279; 65.6%) underwent a bypass procedure (proximal Roux-en-Y, *n* = 168, and OAGB/MGB, *n* = 15) and 74 patients (26.5%) had a sleeve gastrectomy. Patients' data are shown in Table 1.

Table 1. Patient data

	RYGB	SG	OAGB/MGB	BPD-DS/BPD/SADI-S	GB VBG
<i>n</i> 279 (F223/M56)	168 (F142/M26)	78 (F56/M22)	11 (F7/M4)	7 (F7/M0)	15 (F13/M2)
Age (y)	43.88 ± 10.87	45.84 ± 11.11	46.09 ± 9.48	45.86 ± 9.84	46.80 ± 9.26
Height (cm)	166.84 ± 7.93	169.91 ± 10.04	170.14 ± 8.11	166.57 ± 6.65	166.73 ± 9.28
Weight at surgery (kg)	140.88 ± 26.91	159.35 ± 30.58	165.45 ± 29.97	172.00 ± 34.08	152.93 ± 35.78
Weight at examination (kg)	100.03 ± 26.64	120.15 ± 34.26	112.89 ± 34.09	108.91 ± 15.91	126.20 ± 25.42
BMI (kg/m ²) at surgery	50.68 ± 9.02	55.14 ± 9.12	57.09 ± 8.75	61.61 ± 8.87	54.85 ± 12.16
Excess weight at surgery (kg)	74.0 ± 25.0	89.45 ± 26.53	95.32 ± 26.94	105.43 ± 29.38	86.20 ± 32.52
EWL (%)	57.27 ± 29.28	46.26 ± 26.35	56.12 ± 31.95	55.11 ± 23.89	22.00 ± 45.69
TBWL (kg)	40.92 ± 21.87	39.20 ± 23.44	52.56 ± 33.07	63.09 ± 43.40	26.73 ± 27.12
TBWL (%)	28.75 ± 14.20	24.95 ± 13.70	31.18 ± 17.81	34.11 ± 16.93	15.07 ± 18.69
Time-elapse from surgery to examination (months)	54.28 ± 38.54	27.78 ± 21.71	16.45 ± 15.46	42.14 ± 17.24	173 ± 52.71

RYGB: roux-en-Y gastric bypass; SG: sleeve gastrectomy; BPD: biliopancreatic diversion; GB: gastric banding; VBG: vertical banded gastrostomy; EWL: excess weight loss; BMI: body mass index; OAGB/MGB: one-anastomosis/mini gastric bypass; Sadi-S: Single anastomosis duodeno-ileal bypass with sleeve gastrectomy; TBWL: total body weight loss; BPD-DS: biliopancreatic diversion with duodenal switch

Procedure data

The medium time from primary surgery to introduction was 51.34 ± 46.85 months in the overall cohort ($n = 279$). Eleven patients ($n = 11$) presented with rarer and more dated procedures, including GB and VBG. In those patients, time between surgery and re-evaluation due to complaints was 173.20 ± 52.71 months. All those bariatric procedures other than RYGB or SG were combined and added to this third subgroup, including GB, VBG (together $n = 15$), BPD ($n = 7$) and OAGB/MGB ($n = 11$) procedures (total $n = 33$). Analysing the other two main subgroups - RYGB and SG - demonstrated a highly significant difference in the time between surgery and reported complaints. Time span to the actual reported emergency-evaluation was 54.3 ± 38.6 months after a RYGB and 27.8 ± 21.7 months after SG ($P = 0.0001$).

Complaints - weight regain

The vast majority of patients reported non-specific worsening abdominal pain, which was the most common indication for examination. However, a closer exploration often revealed the most feared patient concern, which is weight regain (49.82%; 139/276) regardless of the severity of the existing complaints. This additionally affected 61 patients after SG (78.20% 61/78) and 65 patients after RYGB (38.7%; 65/168). The medium gastric volume of the 3D volumetry was 174.41 ± 59.36 mL in SG and 47.91 ± 20.86 mL in RYGB. The Pearson's chi-square value was calculated for all SG volumes and the contemporarily related EWL. A bilateral signification of 0.005, ($P < 0.01$) as inverse relation was found between volume and EWL with a confidence level of 99%.

GERD and hiatal hernia

GERD was another frequently reported symptom, which affected predominantly patients with SG (39/78; 50%), VBG, GB and BPD (in total, 52/279; 18.63%). After sleeve gastrectomy, 3D-CT revealed in 47.29% (35/74) a hiatal hernia, whereas, following RYGB, hiatal hernias were detected only in 16.07% (27/168). It is noteworthy that there was no significant difference in the detection rate or the longitudinal quantitation of a hiatal hernia, when the results of endoscopic examination and 3D-CT were compared (2.55 ± 0.82 cm vs. 2.24 ± 1.13 cm in RYGB and 3.04 ± 1.23 vs. 2.69 ± 1.59 in SG). However, especially in difficult cases, the detailed imaged anatomy showed more details, which were easier to reveal, and therefore provided additional and often therapy-critical information. It directly influenced the objectivity of findings and, thus, the decision-making security. Due to the additional information resulting from 3D-CT, which revealed a twisting, relative constriction or a remnant and herniated part of the fundus after SG, 12 of the patients underwent directly conversion to RYGB without previous conservative therapeutic attempt. The major finding was that 3D-CT had direct impact on the resulting patient treatment in more than 21% of cases, without performing another UGI, which had already previously been carried out without success in the referring departments.

Table 2. Results and comparison of upper endoscopy and 3D-CT

	RYGB UE	RYGB 3D-CT	SG UE	SG 3D-CT
Hiatal hernia Longitudinal measure (cm)	2.55 ± 0.82	2.24 ± 1.13	3.04 ± 1.23	2.69 ± 1.59
Volume (mL)		47.91 ± 20.86		174.41 ± 59.36
Diameter of the pouchoutlet (cm)	3.91 ± 0.71	2.16 ± 0.67		

UE: upper endoscopy; 3D-CT: three-dimensional computed tomography volumetry; RYGB: roux-en-Y gastric bypass; SG: sleeve gastrectomy

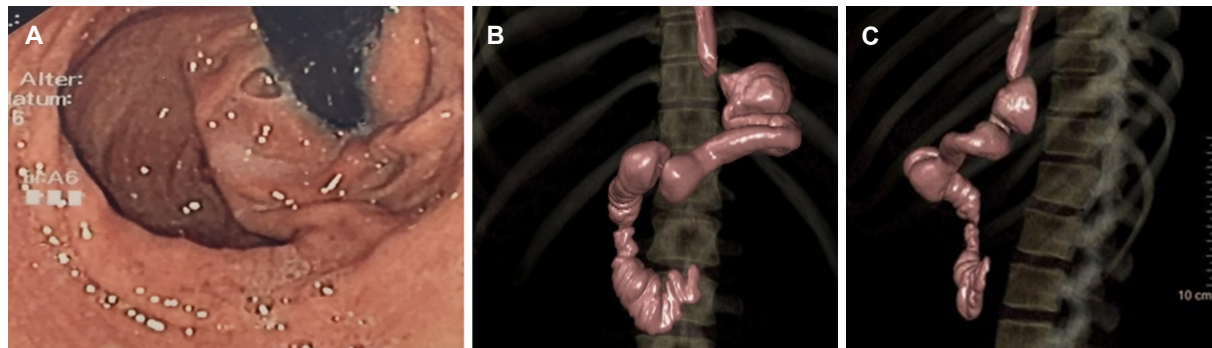


Figure 1. Patient after sleeve gastrectomy with remnant part of fundus, which is herniated to the mediastinum. The sleeve itself is twisted: Endoscopic and 3D-CT view

Pouch-outlet measurement

Another significant difference was found when comparing the diameter measure of the pouch-outlet in patients with RYGB. With 3D-CT, the mean diameter was 2.16 ± 0.67 cm vs. 3.91 ± 0.71 cm with endoscopic measurement ($P < 0.001$) [Table 2].

Clinical cases as visual exemplification of the results

Case 1

A patient after SG with a remnant fundus, which herniated secondarily to a para-oesophageal position. After an odyssey of diagnosis and therapy attempts, the patient was referred in malnourished condition and with recurrent insatiable vomiting and regurgitation. The endoscopic passage was possible without any problems; several external UGIs and even CT scans could not give a decisive clue [Figure 1A-C].

Thus, the indication for examination was the detective assessment of possible underlying anatomical peculiarities. UE already showed the paraesophageal herniation, but could not demonstrate the directly subdiaphragmatic located first bend of the S-shaped kinking. Imaged by 3D-CT, the adjunctive and crucial anatomical details were firstly a SG double-twist, beginning shortly beyond the diaphragm and secondly the accurate position and tightness of the cardia in relation to the herniation, both exiguous details that were missed during UE and previous external UGIs. According those findings, immediate adhaesiolysis, rest-fundus resection and conversion to RYGB was scheduled after two years of complaints.

Case 2

A patient after SG with a subtotal stenosis at the angulus fold, which was not easily passable during UE. UGI had shown the very tight stenosis, but only 3D-CT revealed the enormous extent of dilatation of the antrum. The treatment algorithm would have primarily indicated an attempt of dilation. This was dispensed not only because of the tightness of the stenosis, but especially because of the enormous dilatation of the antrum, which needed surgical re-resection [Figure 2A and B].

The patient underwent direct conversion to RYGB.

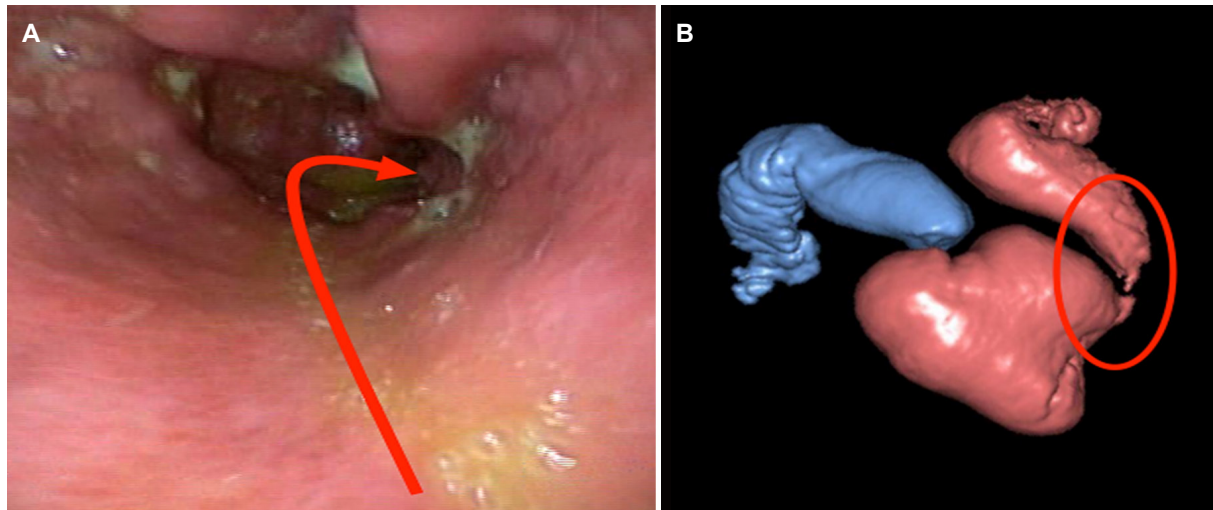


Figure 2. Patient after sleeve gastrectomy with a subtotal stenosis at the angulus fold. Endoscopic and 3D-CT view

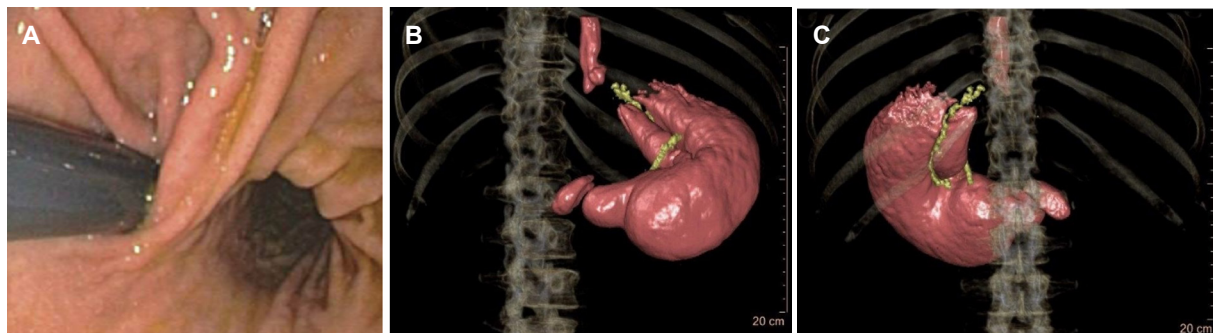


Figure 3. Patient after vertical banded gastroplasty. Endoscopic and 3D-CT view

Case 3

A patient after VBG. The indication for examination was weight regain and non-specific pain in the upper abdomen. Resection lines for the conversion to RYGB were planned with regard to the 3D-CT, which showed perfectly the positioning of the Silastic ring and the length of the vertical partition staple line [Figure 3A-C].

Cases 4 and 5

Implants and their anatomical position can be surround-viewed from all angles and sides, due to full 360° rotatability of the images [Figures 4 and 5].

Case 6

A patient after RYGB. Fully distended Candy Cane, visible from different angles [Figure 6A and B].

DISCUSSION

Besides the very detailed anatomical pictures, as shown above, which are invaluable as indication and surgery planning guidance in complex revisional surgery, by far the most convincing advantage of 3D-CT is the additional possibility of volumetry.

Weight regain is of special concern in bariatric patients and effective therapy necessitates an objective measurement of gastric volume. Concordantly, our results and the recent results of Hanssen *et al.*^[9] clearly

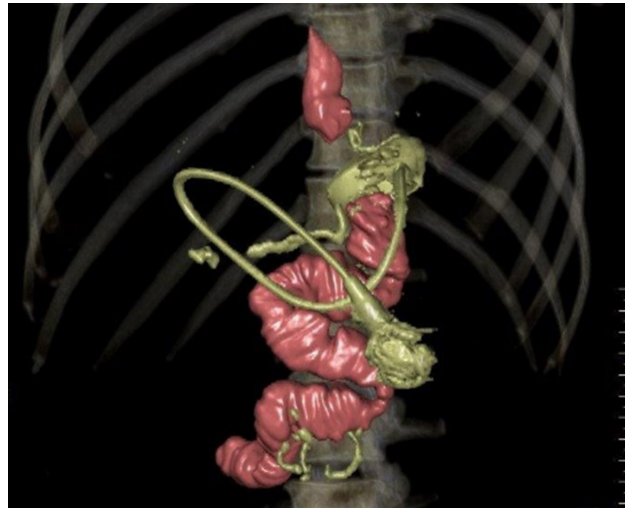


Figure 4. Banded bypass

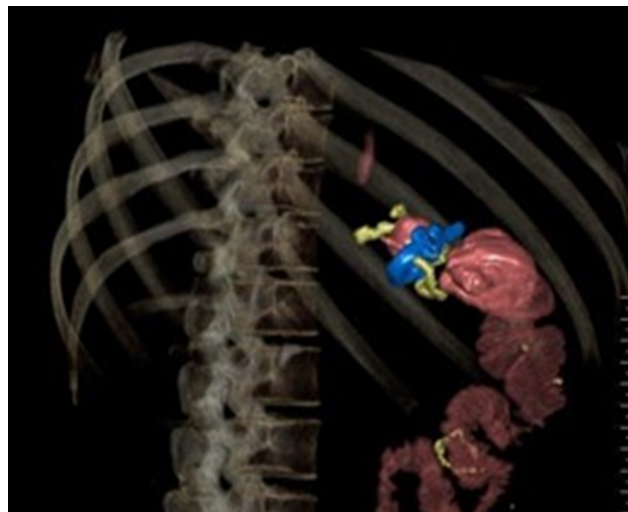


Figure 5. Roux-en-Y gastric bypass with minimiser

demonstrate that SG volume plays a decisive role in weight management (initial weight loss, weight loss failure and possible weight regain). Weight regain is the most feared concern not only in bariatric patients. Actually, SG is globally the most applied bariatric procedure and weight regain occurs frequently after this procedure. 3D volumetry might be a new focus of diagnostic interest for two reasons. Firstly, it shows a rotatable 3D model of the stomach and its attached structures, even under the most difficult anatomical conditions. In addition, it allows a precise and highly reproducible evaluation of volume alterations of the stomach.

3D-CT is the only accurate diagnostic option available for these purposes. Different bariatric procedures and different surgical techniques lead to varying outcomes, which present challenges pertaining to the evaluation of post-surgical volume and gastro-intestinal (GI) anatomy, especially in regard to the comparability of former, contemporary and future examinations. For this purpose, a protocol should be followed that provides standardised procedural principles for all examinations, thus granting comparability of the results. A diagnostic algorithm is shown in [Figure 7](#).

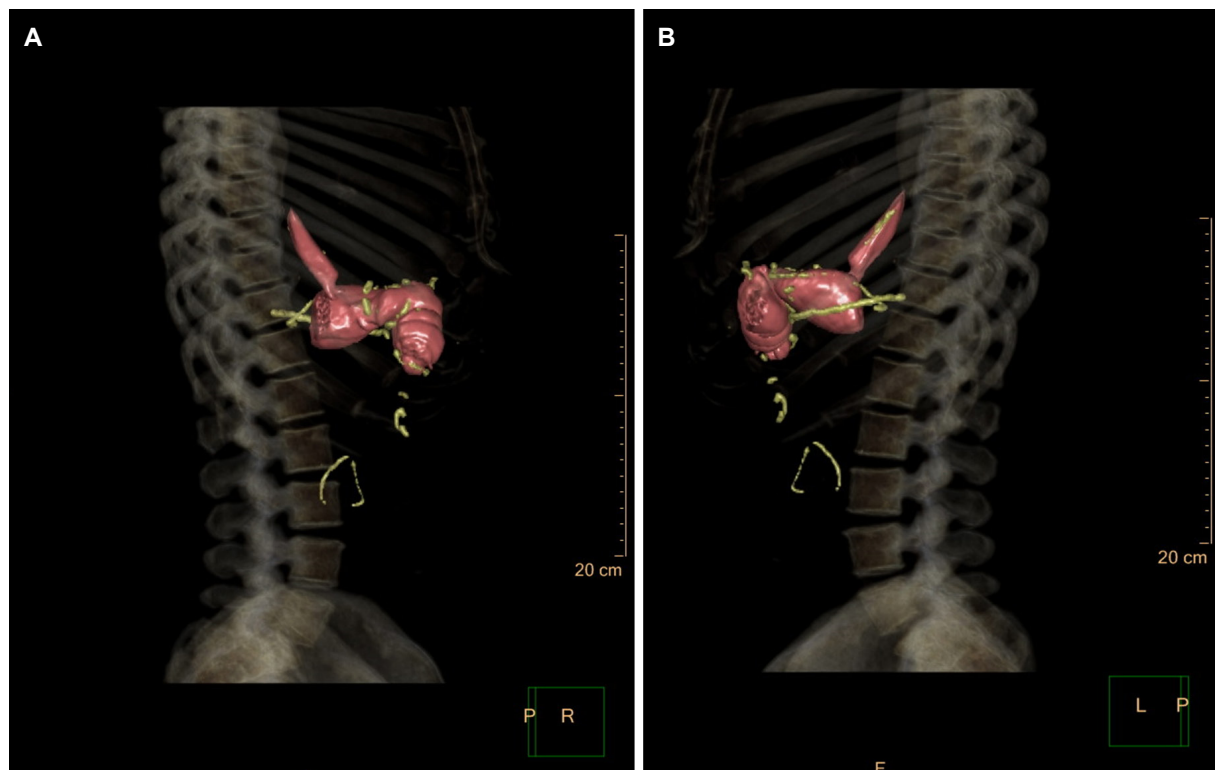


Figure 6. Patient after roux-en-Y gastric bypass. 3D-CT shows the fully distended candy cane in a 360° view

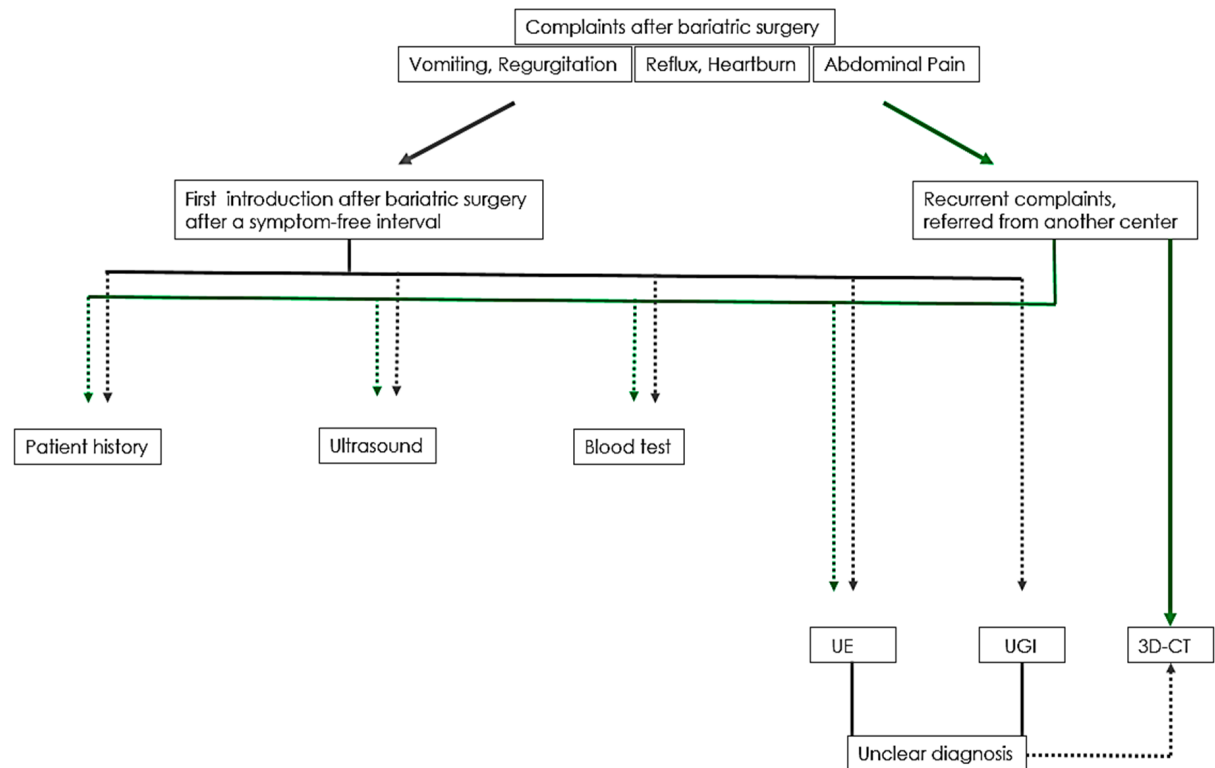


Figure 7. Diagnostic algorithm

It remains undisputed that, in early perioperative complication management, with special regard to the detection of leaks or stenosis, UGI is the first choice of diagnostic measures. While UE serves as a useful routine examination in patients presenting with upper GI symptoms, 3D-CT allows additionally a more detailed evaluation of post-procedural gastric anatomy and its adjacent structures, enabling easier detection and differentiation of longer-term complications such as sleeve dilatation or thoracic migration^[10-14]. In sleeve dilatation, a tight sleeve diameter at the angulus fold may cause dysphagia, regurgitation and vomiting after food intake comparable to the symptoms of a hiatal hernia with tight cardia. Thus, thoracic migration is less frequently associated with pure oesophageal reflux symptoms and heartburn. Functional SG stenosis may result in pre-stenotic dilatation of the proximal part of the sleeve. In both entities, 3D-CT imaging is a very useful adjunctive diagnostic tool. It shows the functional anatomy that a highly experienced bariatric endoscopist also might be able to notice, but 3D-CT represents the anatomy as examiner-independent, objective imaging.

A further distinct advantage of 3D-CT is the clear depiction of implanted devices (e.g., bands), and their precise anatomical position, which is not possible with UGI due to the lack of tissue extension during the examination.

Additionally, in this study, we evaluated and compared the results of UE with those of 3D-CT for the measurement of the pouch outlet. In contrast, 3D-CT is not the diagnostic tool of choice for that purpose.

In almost all cases, the diameter of the Pouch outlet during 3D-CT appeared smaller than was indicated by direct measurement during endoscopy ($P < 0.001$). This may result from the different extension pressures applied during the respective examinations: whereas, in 3D-CT, the foaming effervescent powder creates enough pressure to gently distend the gastric wall, direct air inflation via endoscope, positioned directly above the anastomosis, causes considerably greater distention. Remarkably, therefore, the pouch outlet after RYGB was significantly underestimated in the examination with 3D-CT.

This is of particular significance in cases of dumping syndrome, a known long-term complication of RYGB, which is often related to an enlarged pouch outlet. For planned outlet reduction procedures in these patients, UE remains the diagnostic tool of choice^[15].

From an economical point of view, the costs of 3D-CT are only slightly higher than those of UGI, with current costs of 162.50 euro vs. 225 euro, as calculated by the state health insurance point system in Germany. An additional contrast to the effervescent powder is not necessary for the examination.

3D-CT images reveal three-dimensional information, which is unattainable by alternative examination methods, and allows precise location of the anatomical structures of the upper GI tract. While shape and volume measurements of SG may be repeatedly assessed using this method, the optimal volume of SG or pouch in RYGB remains as yet undefined, but Hanssen *et al.*^[9] recently showed the benefit of a volume ≤ 100 mL^[10]. The patients in our SG group had an average volume of 174.41 ± 59.36 mL at a reported rate of weight regain of 78.20%. At least this seems to prove that a volume of 174.41 mL is too large to maintain the gastric restriction and thus leads to a loss of satiety.

3D-CT scan offers a superior technique for the evaluation of volumetric questions, whereas two-dimensional measurements, such as the objectively verifiable diameter of an anastomosis or stenosis, are obviously better assessed by direct measurement with endoscopy.

3D-CT examination requires a bariatrically trained radiology team with a standardised protocol for best results, as described above.

This study is limited by the retrospective nature of the data analysis. In addition, the data were collected in a single-centre study, although 3D-CT is a well-established diagnostic tool in this high-volume certified centre of excellence for obesity and metabolic surgery.

To conclude, 3D-CT is quick, easy-to-perform and facilitates identification of the post-surgical gastric anatomy. It represents a valuable additional diagnostic tool in post-bariatric patients with post-procedural complications, since UE and UGI might miss the three-dimensional post-bariatric anatomy. 3D-CT might be an important preoperative tool prior to revisional surgery and an ideal diagnostic complement in patients with post-surgical complications following obesity surgery.

DECLARATIONS

Authors' contributions

Designed the article: Stier C, Chiappetta S

Calculated the statistics and proofed the concept: Parmar C, Koschker AC, Stier R

Operating radiologist: Bokhari M

Availability of data and materials

Data route from the results of routine examinations of patients. Anonymized data sheet is available from the authors (Stier C).

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

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Review

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Transanal minimally invasive surgery: how can it help us?

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Abstract

Transanal surgery has evolved significantly in the past few decades. With the technological advancements of endoscopic systems, minimally invasive approaches in transanal surgeries are quickly increasing in popularity. Transanal endoscopic microsurgery was developed initially with subsequent transanal minimally invasive surgery (TAMIS) being introduced as an alternative in 2009. Over the past decade, more and more papers have been published on TAMIS, regarding the management of benign/malignant rectal lesions as well as repair of anastomotic leaks, anastomotic strictures, rectovaginal/rectourethral fistula, *etc.* This review details the progress of transanal surgery and the use of TAMIS in different scenarios.

Keywords: Transanal minimally invasive surgery, transanal surgery

INTRODUCTION

Previously, rectal lesions, both benign and malignancies, were initially managed with local transanal excision (TAE) with the assistance of anal retractors (Park's transanal technique). This approach has its limitations, such as poor visibility, fragmented specimens, and difficulties in accessing proximal two-thirds lesions^[1]. Subsequently, transanal endoscopic microsurgery (TEM) was introduced to overcome the drawbacks of TAE. TEM has shown to be superior to TAE, resulting in less fragmentation and better quality of excision. TEM also shows lower incidences of local recurrence in well-selected T1 rectal cancer^[2,3]. However, this technique was not well adopted due to its high cost and steep learning curve.

Transanal minimally invasive surgery (TAMIS) was introduced in 2009 and in the span of a few years gained multiple international experiences. TAMIS is defined as the use of any multichannel port



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transanally together with standard laparoscopic camera and a standard CO₂ insufflator. This approach has now been well accepted as it does not incur additional costs and has a lower learning curve. Besides aiding in excision of rectal lesions, this method has been adopted for a variety of other procedures such as transanal total mesorectal excision (TME), repair of rectovaginal/rectourethral fistulas, repair of anastomotic complication after low anterior resection, *etc.* This review details the progress of transanal surgery and the use of TAMIS in different scenarios.

TAMIS FOR LOCAL EXCISION OF RECTAL LESIONS

Since Park technique was first described in 1968, approaches for local excision of rectal tumors have undergone many changes. TAE evolved to TEM, which was first described by Buess *et al.*^[4]. However, this approach was not popularized due to the cost and the steep learning curve. With the advancement in natural orifice transluminal endoscopic surgery, TAMIS was introduced in 2009^[5]. Now, TAMIS is a reasonably good platform for the local excision of multiple rectal neoplasms, such as benign adenomas, lesions with high grade dysplasia, neuroendocrine tumors, and well-selected malignant rectal lesions.

INDICATION

The indications for TAMIS do not differ from those of TAE or TEM for both benign and malignant lesions that have been assessed preoperatively with endoscopy and complimented by endoanal/endorectal ultrasonography and/or magnetic resonance imaging^[6-8]. For benign lesions, it could be large adenoma, high grade dysplasia, or incompletely excised lesion through colonoscopy. For malignant lesions, early rectal cancers that are confined to the submucosal layer (T1 lesions) are best suited for TAMIS.

T1 adenocarcinoma of the rectum can be categorized into low-risk lesions and high-risk lesions based on the risk of recurrence/metastasis. This can be further categorized into low-risk T1 adenocarcinomas of the rectum, which are described as small lesions less than 4 cm in diameter; Haggits 1-3 lesions; Kikuchi sm1 lesions; and well-differentiated cancer with no lymphatic, vascular, or perineural invasion^[6]. High-risk lesions are Haggits 4; Kikuchi sm2/sm3, poorly differentiated tumors; signet cell lesions; presence of tumor budding; lymphovascular involvement; absence of lymphoid infiltration; and young patients (< 45 years old). This is due to T1 lesions having risk of LN metastasis of up to 10%-15%. However, with sub analysis, sm1 lesions only carry 1%-3% risk of lymph node (LN) metastasis while the risk increases to 8% for sm2 lesions and 23% for sm3 lesions. Similarly, Haggits 1-3 lesions have less than 1% risk of lymph node metastasis, while, for Haggits 4 lesions, the risk is about 12%-15%. Hence, high-risk lesions should ideally be treated as T2 lesions^[7,8] and they should be discussed in multi-disciplinary team meetings for a holistic approach of management.

It is sometimes difficult to distinguish T1 or T2 lesions preoperatively, and, for these, TAMIS could be a platform for the resection of these lesions and guide the further management based on the final pathology report. Hence, it is wise to counsel these patients on the possibility of formal radical resection if the pathology report is unfavorable, high-risk T1 or T2 lesions. TAMIS resection could also be an option for palliation for T3 tumors when patients are unfit to undergo a radical resection.

SAFETY AND FEASIBILITY

Multiple studies have been published on the safety and feasibility of TAMIS^[5,9-17], with Albert and Atallah publishing one of the biggest series. They reported an overall loco-regional recurrence rate of 4.3%, with positive margins of 6% in their 20-month follow up study^[16], whereas Keller and Haas reported 6.6% of their patients with positive margin and only one patient had local recurrence at median follow up of 39.5 months^[13].

Penetration into the peritoneal cavity is unavoidable during local excision of malignant lesions that are located at the anterior wall of the upper rectum (above the peritoneal resection). Chen *et al.*^[18] reported

about 16% of peritoneal entry for lesions at the upper rectum. During local excision of malignant lesions, it is necessary to excise the lesion in full thickness as there is a possibility of an invasive component^[19]. Not surprisingly, partial excision will lead to significant positive margins, which translates to loco regional recurrence^[20]. Dufresme *et al.*^[21] described the usage of a laparoscopic stapler for excision of high rectal sessile polyps as an approach to prevent peritoneal breach. However, the evidence supporting this approach is only backed by a short series of five cases.

LEARNING CURVE FOR TAMIS

Assessing the surgical technique competency in TAMIS, Maya *et al.*^[22] reported that four cases are adequate. Chen *et al.*^[18], however, mentioned that at least 10 cases are necessary to obtain proficient skills. Clermonts *et al.*^[23] stated that a standardized institutional protocol with proficient proctorship could lead to a shorter learning curve with only 6-10 cases, but ideally 18-31 cases, being required.

WHICH IS BETTER?

TEM and TAMIS have been compared in multiple papers. Lee *et al.*^[24] reported that there are no statistical differences in the quality of obtained specimens, peritoneal entry, postoperative complications, five-year disease free survival, and incidence of local recurrence for those who did not undergo salvage surgery. After analyzing 428 patients (247 with TEM and 181 with TAMIS), it was concluded that the cost, availability, and surgeon's preference should determine the choice of the platform.

TAMIS FOR PROCTECTOMY AND TRANSANAL TME

Standardization of TME as well as the selective use of chemoradiotherapy has brought significant improvement in the management of rectal cancer^[25]. Local recurrence rates have dropped to < 6% when TME is performed with negative circumferential resection margin and distal resection margin, together with neoadjuvant radiotherapy. The local recurrence was as high as 45% without TME and dropped to 10% with TME alone^[26,27].

The first laparoscopic-assisted TME was performed on a 76-year-old woman with rectal cancer in 2009. Since then, multiple articles have been published on TME. The concept of TME came into existence due to the ease in reaching the distal rectum, which would otherwise be technically challenging with the conventional transabdominal TME approach, especially for patients with high body mass index, narrow male pelvis, or bulky low rectal tumors. Indirectly, this leads to a lower conversion rate and better pathological outcomes (distal margin) compared to the transabdominal approach^[28]. A meta-analysis by Jiang *et al.*^[29] demonstrated that TME leads to longer circumferential and distal resection margins. This approach also reduces the risk of positive circumferential margin.

However, a Norwegian team reported an unexpectedly high local recurrence after TME (9.5%)^[30] but data from two of The Netherlands' high-volume hospitals reported otherwise. Their data show local recurrence of only 3.8% over a mean follow up of 54.8 months^[31]. The currently undergoing GRECCAR 11 and COLOR III randomized control trials will be able to elucidate the long-term oncological outcomes of low and mid rectal cancer with the transanal approach^[32].

TAMIS FOR LATERAL PELVIC NODE DISSECTION AND PELVIC EXENTERATION

Lateral pelvic lymph node (LPLN) metastases in patients with colorectal cancers are usually seen in advanced cases. Some studies have shown neo-adjuvant chemoradiotherapy to be inadequate and a surgical approach remains an option to be considered^[33,34]. Laparoscopic LPLN dissection is technically challenging, especially in obese patients with narrow pelvis. It is difficult to access those lymph nodes at the inferior margins of the lateral pelvis via laparoscopic approach. Aiba *et al.*^[35] and Zeng *et al.*^[36] demonstrated

that transanal LPLN dissection is feasible, safe, and promising in well-selected patients. Hayashi *et al.*^[37] published that pelvic exenteration is also possible with the TAMIS platform.

TAMIS FOR EXCISION PERIRECTAL LESIONS

Excision of perirectal/pararectal lesion can be difficult even with open techniques due to the narrow space and low accessibility. The lesion frequently needs to be excised together with the rectum. TAMIS can be used to excise pararectal/perirectal lesions without the need for proctectomy or abdominal perineal resection. McCarrol and Moore^[38] reported their success in excising a retro rectal cyst (tailgut cyst) in a 23-year-old patient. Furthermore, TAMIS has also been used for the excision of rectal GIST^[39,40].

TAMIS FOR COMPLICATION OF LOW RECTAL ANASTOMOSIS

Anastomotic leak after a low anterior resection can be devastating. These patients often require repeat surgery and it is usually laparotomy. However, with high degree of suspicion and early intervention, these complications could be handled with minimally invasive approaches as well. Chen *et al.*^[41] reported on methods to manage anastomotic leaks post anterior resections using laparoscopic lavage and transanal endoluminal repair on transanal endoscopic operation platform. Patients, in whom the anastomotic leak was detected early (within five days), did not require conversion to laparotomy and were able to be discharged promptly. Olavarria *et al.*^[42] reported a case managing presacral abscess post anastomotic leak through three sessions of septotomies and debridement through TAMIS before successfully reversing the ileostomy. In a completely occluded anastomosis after a low anterior resection, Bong and Lim^[43] managed to excise the fibrotic tissue at the stenotic site and regain the continuity of the canal.

CONCLUSION

TAMIS is an evolving surgical approach and should remain an option to be considered in the management of patients. With an increasing number of surgeons becoming familiar with TAMIS procedures, the indication for this approach expands. However, a structured training program including proctoring to ensure safe implementation of the procedure is necessary for beginners to obtain the necessary skills to prevent unnecessary complications, as this is still a relatively new approach.

DECLARATIONS

Authors' contributions

Contributed in the literature search and write up: Sriram RK

Contributed in literature search, corrections and proof reading: Chen WTL

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Robotic transanal surgery: perspectives for application

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Abstract

Transanal minimally invasive surgery (TAMIS) is a surgical technique which allows the local excision of rectal benign tumors and early stage cancers measuring up to 4 cm and lying within 6-8 cm from the anal verge. It is performed by means of a disposable transanal platform and conventional laparoscopic instruments, proving to be effective and easily available. Hence, TAMIS soon became a valid alternative to other transanal resective procedures, especially transanal endoscopic microsurgery, and rapidly spread. Moreover, soon after its introduction, TAMIS started to be performed also using robotic technologies, but no clear advantages were found to date. This review is intended to provide a general overview on TAMIS, with a special focus on its association with robotic systems and the perspectives of this approach.

Keywords: Transanal minimally invasive surgery, robotic transanal minimally invasive surgery, robotic transanal surgery

INTRODUCTION

Benign tumors and early stage cancers of the rectum measuring less than 4 cm and lying within 6-8 cm from the anal verge represented for a long time an indication for conventional transanal excision (TAE)^[1]. This technique was performed under direct view using a rigid anoscope and conventional surgical instruments. However, inadequate exposure was quite usual, especially when lesions were located in the middle or



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upper rectum, which frequently appeared inaccessible^[1,2]. That often compromised the quality of surgical resection^[1,2], with a rate of positive margins higher than 10% even in the series of the most experienced surgeons^[3,4].

The attempt to overcome the limitations of TAE stimulated the development of transanal endoscopic microsurgery (TEM). Introduced in the early 1980s by Buess *et al.*^[5], this technique involved the use of three main components: a specific rigid proctoscope, a dedicated camera, and modified laparoscopic instruments. In particular, the rigid proctoscope was fixed to the operating table, oriented by the surgeon, and provided with several ports for pneumorectum creation, smoke evacuation, the camera, and instruments. Operative steps were quite similar to TAE, and the surgical wound resulting from full- or partial-thickness wall resection could be left open or closed by several techniques (such as sutures or clips).

Compared to TAE, TEM allowed an easier resection of rectal tumors lying in the middle or upper rectum, making excision possible even in some cases of lower sigmoid colon lesion^[6]. Moreover, several studies showed better outcomes after TEM^[3,7-10]. Notably, a systematic review with meta-analysis published by Clancy *et al.*^[8] in 2015 reported significant differences in terms of negative resection margins, specimen fragmentation, and local recurrence in favor of TEM, whereas the postoperative complication rate was similar between conventional TEM and TAE.

However, TEM showed to have some important limitations. Notably, the dedicated surgical equipment was designed for an up-to-down approach to rectal lumen. That made the resection of anterior rectal lesions quite challenging, requiring to place the patient in a prone position and to use specific split-leg operating tables. Moreover, the necessary surgical material was expensive and the learning curve long. Hence, the implementation of TEM remained limited^[1,2].

To provide an alternative to TEM for local excision of rectal tumors, in 2009, an American surgical team from Florida introduced a new technique called transanal minimally invasive surgery (TAMIS)^[11].

The present study is intended to provide a general overview on TAMIS, summarizing its most important aspects and focusing on the association with robotic technology and its implementation.

TAMIS: TECHNICAL ASPECTS AND INDICATIONS

TAMIS is a surgical technique introduced by Atallah, Albert, and Larach in 2009 to provide an alternative to TEM for local excision of rectal neoplasia^[11].

It combines the use of a disposable multichannel port placed transanally with conventional laparoscopic equipment. Notably, the pneumorectum is achieved using common laparoscopic systems inflating CO₂, and the endoluminal pressure ranges between 15 and 25 mmHg^[1]. A 30°- or 45°-angled 5-mm laparoscope is preferable^[12,13], whereas conventional laparoscopic instruments are used for manipulation. Initially, single-site multichannel ports conceived for laparoscopic abdominal surgery were adapted to a transanal use. Later, several devices were specifically designed^[12-14].

TAMIS is indicated for the local excision of a number of benign and premalignant tumors of the rectum located at up to 15 cm from the anal verge^[15-19]. This technique may also represent a curative treatment for selected patients with rectal cancer. Notably, according to the National Comprehensive Cancer Network guidelines 2018^[20], transanal local excision may be an appropriate therapeutic option in case of early-stage T1 tumors with small size (< 3 cm), well to moderate differentiation, location within 8 cm from the anal verge, and extension to less than 30% of rectal circumference. The resection must be full-thickness and assure more than 3-mm negative margins. The specimen must be oriented and pinned before fixation. In the

case of negative pathological features, such as positive resection margins, lymphatic and vascular invasion, poor differentiation, or Kikuchi sm3 level, a more radical resection is needed. Moreover, TAMIS could also be indicated in the case of more advanced T-stage rectal cancer in order to provide an excisional biopsy for a more precise pathologic examination or to treat patients at high surgical risk in association with other treatments^[13,14].

The principles of local resection are similar in TEM and TAMIS. First, the lesion must be marked around its circumference. Benign tumors may be excised limiting the dissection to the submucosal layer, without need to close the surgical wounds^[13]. On the contrary, malignant tumors require a full-thickness resection of the rectal wall^[13]. Moreover, in the case of posterior tumors, a small amount of perirectal fat may be excised *en bloc* to ensure a complete excision and allow lymph node analysis^[13].

When rectal tumors are located posteriorly, it would not be necessary to close a full-thickness defect because of its extraperitoneal position, as suggested by several authors reporting no higher complication rate after leaving surgical wounds open^[13,21]. However, this time-consuming practice is recommended to cover an eventual peritoneal entry^[13,22]. In particular, the wall defect is generally closed transversely, using separated or running sutures, clips, or other devices^[1,13]. Peritoneal entry represents a well-known complication of TAMIS and it is described more frequently when tumors are located anteriorly in the middle or upper rectum^[12]. When it occurs (1% of cases^[12]), it is recommended to use a steep Trendelenburg position to facilitate wall repair and to convert to laparoscopy if it is impossible to maintain an adequate pneumorectum^[22-24]. With this regard, some authors suggest placing the patients in a prone position to limit the amount of CO₂ passing into the peritoneal cavity^[25]. Among the postoperative complications of TAMIS, a rectovaginal fistula can also occur, besides common general surgery complications, such as bleeding (2.8%)^[12], fever, urinary tract infections, and atrial fibrillation.

TAMIS: OUTCOMES

In 2014, Martin-Perez *et al.*^[12] published a systematic review of the literature about TAMIS, including 24 retrospective studies and 9 case reports. The authors reported that up to eight alternative abbreviations were used to indicate the same technique, and included overall 390 patients, undergoing TAMIS for malignant lesions in 209 cases (53.5%), adenomas and high-grade dysplasia in 152 cases (39%), and other pathology in 29 cases (7.5%). Among these latter 29 cases, 23 patients (79.3%) were operated for neuroendocrine lesions, 3 patients (10.3%) for fibrosis, 1 patient (3%) for GIST, 1 patient (3%) for mucocele, and 1 patient (3%) for melanoma. Surgical procedures were performed using eight different TAMIS platforms, among which SILS port was the most commonly used (66.7% of all studies included). The mean size of resected lesions was 3.1 cm (range: 0.8-4.7 cm), whereas the mean distance from the anal verge was 7.6 cm (range: 3-15 cm). The authors reported only full-thickness excisions in 22 studies (60.6%), only partial thickness excisions in 3 studies, both full-thickness and partial thickness excisions in 8 studies (24.2%), and no precision about the extent of resection in 5 studies (15.2%). Conversion rate to TAE, TEM, or abdominal laparoscopic surgery was 2.31% (9/390). The mean operative time was 76 min (range 25-162 min), the complication rate was 7.4%, and the mean hospital stay was two days. Considering the publications reporting specific information about surgical resection quality, the rates of positive resection margins, specimen fragmentation, and recurrence were 4.36% (12/275), 4.1% (4/97), and 2.7% (7/259), respectively.

TAMIS VS. TEM

In the literature, several studies compared the outcomes of TAMIS and TEM^[26-28]. Among them, it is important to consider the large multi-institutional matched prospective study published by Lee *et al.*^[28] in 2017. It included 181 patients undergoing TAMIS and 247 patients undergoing TEM, and showed that

TAMIS was associated with shorter operative time (mean: 70 min vs. 108 min), shorter length of hospital stay (median: zero days vs. one day), and lower blood loss (median: 10 mL vs. 30 mL) compared to TEM. However, no significant difference was found in terms of positive margins (7% for TAMIS vs. 6% for TEM), specimen fragmentation (4% for TAMIS vs. 3% for TEM), postoperative complications (9% for TAMIS vs. 11% for TEM), and recurrence after resection for rectal malignant lesion (7% for TAMIS vs. 7% for TEM). Overall, the authors concluded that, given the absence of significant differences in terms of resection quality and postoperative morbidity, the choice of the technique should be based on surgeon's preference, availability of surgical materials, and costs.

Two further comparative studies were both published in 2016^[26,27]. Notably, compared to TEM, TAMIS had shorter median hospital stay (four days vs. five days) but lower full-thickness resection rate (85% vs. 100%) according to Mege *et al.*^[26] and higher specimen volume (mean: 5.6 cm³ vs. 15.9 cm³) according to Melin *et al.*^[27]. No other significant difference between TAMIS and TEM was found in terms of operative, pathological, and survival outcomes.

In 2019, Van den Eynde *et al.*^[29] published another retrospective comparative study, including 68 patients in the group TAMIS and 53 patients in the group TEM. No conversion was reported in both groups. Operative time was again significantly shorter for TAMIS (median: 45 min vs. 65 min), whereas lesion surface area was larger for TEM (median: 21 cm² vs. 14 cm²). The difference in operative time persisted after correction for lesion surface area. No other significant difference was found in terms of quality of resection, morbidity, and hospital stay. Finally, the authors concluded in favor of TAMIS, whose shorter hospital stay was explained by an easier set-up and a greater versatility of the transanal platform. Moreover, the main advantage of TAMIS was identified in the fact that all procedures could be performed in lithotomy position, the whole rectal circumference being accessible with this technique.

To be noted, several studies also analyzed the learning curves of TAMIS and TEM, reporting an improvement of operative efficiency after 14-24^[30] and 18-31^[31] procedures for TAMIS, and after 16^[32] procedures for TEM. However, no comparison was performed in this regard.

Overall, the available studies do not show a clear superiority of TAMIS over TEM, especially in terms of resection quality, which appear similar. However, several technical advantages making TAMIS preferable are reported in the literature^[1,2,13]. In particular, the use of a shorter shaft and a more flexible platform allows surgeons to reach all quadrants of the rectum, and to perform surgery in lithotomy position also in the case of anterior or lateral lesions. Moreover, TAMIS allows a faster set-up (2 min vs. up to 30-45 min^[13]) and a 360° visibility (220° for TEM), involving the use of less expensive and more easily available equipment, such as conventional laparoscopic instruments.

ROBOTIC TRANSANAL SURGERY

The technical advantages provided by surgical robotic systems, such as stable 3D view and ameliorated manipulation, appeared to overcome some ergonomic limitations of TAMIS. Therefore, the same authors who had previously introduced this technique described the first combined use of robotic technology and TAMIS platforms for local transanal excision in a cadaveric model in 2011^[33], and then in a real patient in 2012^[34].

Notably, the first patient undergoing a procedure of robotic transanal surgery or robotic TAMIS (R-TAMIS) was a 58-year-old woman with a 3-cm tubulovillous rectal adenoma with focal intramucosal carcinoma. The tumor was located at 7 cm from the anal verge in the left anterolateral quadrant. The patient was placed in a lithotomy position and a GelPOINT platform was used, in association with a 5-mm laparoscope introduced through one 5-mm port and two robotic arms introduced through two 8-mm ports. A full thickness

resection was performed and the wall defect was closed using a running barbed suture. However, already in this first case report, the authors underlined the high direct cost of the procedure, \$1500, and suggested the use of (R-TAMIS) in complex cases where TEM or conventional TAMIS, often indicated as laparoscopic TAMIS (L-TAMIS)^[2], were not possible.

Since 2012, several studies reporting the outcomes of R-TAMIS were published, but they included many case reports and small series of patients^[2,35-41]. The largest series was published by Tommasi *et al.*^[40] in 2019 and included overall 58 patients. Surgery was performed using a Da Vinci Si system in 40 cases (69%) and a Da Vinci Xi system in 18 cases (31%), whereas a GelPOINT platform was employed in all procedures. A 15-mmHg pneumorectum was created using conventional laparoscopic insufflation systems or an Airseal system. Robotic operative arms were placed at 4 and 8 o'clock positions, with a 0° camera at 12 o'clock. A full-thickness resection was performed for 28 cancers (48.3%), 18 adenomas (31%), 11 carcinoids (19%), and 1 GIST (1.7%), and no conversion was reported. The mean console time was 66.2 min (range: 17-180 min), with significantly shorter mean operative time for Xi robot (38.7 min *vs.* 78.5 min, $P = 0.00003$). Complication rate was 10.3% and overall 52 patients (89.7%) were discharged the same day of surgery. The mean specimen size was 3.3 cm (range: 1.3-8.2 cm). There was no specimen fragmentation in 57 cases (98.3%) and negative resection margins in 55 (94.8%). R-TAMIS proved curative in 51 patients (88%), while 7 patients (12%) needed additional therapy. Finally, the authors generically concluded for the feasibility of R-TAMIS and underlined satisfying oncologic results and better ergonomics.

Some useful data are also provided by the second largest series found about R-TAMIS, published by Liu *et al.*^[36] in 2018 and including 34 patients. All cases reported were performed using a Da Vinci Xi technology and a GelPOINT platform. Surgery was performed for benign lesions in 22 cases (64.7%) and for malignant lesions in 11 cases (32.3%). In 94% of cases ($n = 32$), patients were placed in a lithotomy position. The mean distance of rectal lesions from the dentate line was 8.6 cm (range: 2-15 cm), with a mean maximum diameter of 2.6 cm (range: 0.5-4.5 cm). The overall operative time was 100 ± 70 min (mean \pm SD), including a docking time of 25 ± 14 min (mean \pm SD) and a console time of 76 ± 67 min (mean \pm SD). No intraoperative complication and no conversion were reported. The postoperative complication rate was 3% and the mean hospital stay was $1.18 (\pm 0.83)$ days. Full-thickness R0 resection was achieved in 97% of patients ($n = 33$), three patients were upstaged to T2-stage and underwent anterior resection, and one patient was staged T3. Moreover, the univariate analysis of operative time predictors showed that severe obesity [body mass index (BMI) > 35] was a positive predictor of total operative time and console time, probably because of a narrow space between the legs, whereas specimen size was a positive predictor of total operative time. Finally, the authors concluded that R-TAMIS was safe for lesions located within up to 15 cm from the dentate line and sizing up to 5.5 cm, and that a BMI > 35 was a significant predictor of a longer and more challenging operation.

At least three further series with more than 10 patients were also published, one by Huang *et al.*^[41] in 2019 including 23 patients, one by Gómez Ruiz *et al.*^[37] in 2017 including patients, and one by Hompes *et al.*^[39] in 2014 including 16 patients. In the first study, robotic procedures were performed in a prone jackknife position, whereas, in the latter two, all procedures were performed using a lithotomy position. Note that Hompes *et al.*^[39] reported the use of a glove port, made up of a surgical glove positioned transanally with ports inserted through the glove's fingers.

Moreover, in 2019, Lee *et al.*^[2] published a study including 19 patients undergoing R-TAMIS and reported that patients with anterior and lateral lesions (83.3% of overall included patients) were operated in a prone position in order to reduce the conflict among robotic arms, whereas the lithotomy position was used only for posterior lesions.

L-TAMIS VS. R-TAMIS

Robotic transanal surgery might offer several advantages compared to conventional TAMIS. Notably, it might increase the possibility of resecting rectal lesions located in difficult sites, reducing the need for proctectomy, as well as it might make surgical wound repair easier.

However, only a few studies designed to compare the outcomes of conventional and robotic TAMIS are available in the literature. The most relevant of these is a retrospective study published by Lee *et al.*^[2] in 2019, comparing the results of 21 patients undergoing conventional TAMIS (indicated as L-TAMIS) and 19 patients undergoing R-TAMIS. Overall, no significant difference was found in terms of perioperative outcomes (notably: total operative time, blood loss, postoperative complications, and length of hospital stay) and pathologic findings. The only significant difference was represented by direct costs, which were higher in the robotic group (\$3562 for L-TAMIS vs. \$4441 for R-TAMIS, $P = 0.04$).

TRANSANAL TOTAL MESORECTAL EXCISION

The latest development of the transanal approach to rectal cancer is represented by transanal total mesorectal excision (TaTME). Indeed, laparoscopic rectal surgery may be challenging because of patient- and tumor-related factors. Male obese patients often show a very limited surgical field^[42,43], anterior rectal tumors appear to have a higher rate of positive resection margins^[43,44], and determining the distance between rectal tumor and distal staple line is often difficult^[42].

TaTME is a hybrid surgical technique employed for low rectal cancer combining a laparoscopic dissection for colonic mobilization and a mesorectal excision performed using a transanal approach through a GelPOINT platform or a rigid proctoscope. These approaches may be sequential or simultaneous, the specimen is generally extracted through the anus, and a manual coloanal anastomosis is finally performed^[45]. Several clinical and pathological factors are considered to indicate a transanal approach in the case of rectal cancer: male gender, narrow and/or deep pelvis, BMI > 30 kg/m², prostatic hypertrophy, tumor located at less than 12 cm from the anal verge, tumor size > 4 cm, and tissue alteration following radiotherapy^[46].

Sylla *et al.*^[47] performed the first clinical case of TaTME in 2010. In 2016, Deijen *et al.*^[48] published a systematic review including overall 794 patients with rectal cancer undergoing this technique. The mean operative time was 244 min and the TME specimen was complete in 87% of procedures. Major postoperative complications occurred in 11.5% of patients and anastomotic leak in 5.7%. Local recurrence rate was 8.1% at 18.9 months. A volume effect was also shown, with high-volume centers (> 30 cases) having higher TME quality, lower rate of positive circumferential resection margin (CRM), and lower rate of major complications.

In 2017, Penna *et al.*^[49] analyzed TaTME short-term outcomes using the data of an international registry including 720 patients. TME was complete in 85% of cases, had minor defects in 11% of cases, and had major defects in 4%. The rate of R1 resection was 2.7%. Among the risk factors of suboptimal TME, perforation, and/or R1 resection, the authors also identified a laparoscopic transabdominal posterior dissection to less than 4 cm from the anal verge.

In 2018, Jiang *et al.*^[50] published a systematic review of studies comparing TaTME and laparoscopic TME. They included 762 patients overall operated for cancer of the middle and lower rectum, and showed a significant difference in terms of positive CRM in favor of TaTME, whereas positive distal resection margin and TME quality were similar.

ROBOTIC TATME

TaTME has also been performed using robotic technology, being indicated as robotic TaTME or robotic-assisted transanal TME (RATS-TME). However, the studies on this subject currently available in the literature are characterized by a limited number of patients^[51-55].

Notably, one of the largest was published in 2020 by Hu *et al.*^[56] and included only 20 patients. Eleven of them (55%) were operated for mid rectal cancer and nine (45%) for low rectal cancer. The distance between tumor to anal verge was 6.0 ± 2.7 cm (mean \pm SD), the operative time was 172.3 ± 24.2 min (mean \pm SD), and the blood loss 82.0 ± 107.1 mL (mean \pm SD). No conversion was reported, the postoperative complication rate was 35%, and the length of hospital stay was 8.8 ± 4.2 days. In 90% of cases, TEM was complete, and the number of lymph nodes harvested per specimen was 18.7 ± 6.3 (mean \pm SD). The distal margin length was 3.1 ± 1.3 cm. Positive CRM was found in 15% of cases ($n = 3$).

CONCLUSION

TAMIS represents a valid therapeutic option in the surgical treatment of benign and malignant lesions of the rectum compared to TEM. Robotic transanal surgery soon developed after the introduction of TAMIS and consists in associating the use of robotic surgical systems to transanal disposable platforms. It proved to be safe and effective, but the data currently available in the literature do not show clear statistical advantages compared to conventional TAMIS. Therefore, further studies will be necessary.

DECLARATIONS

Authors' contributions

Conception: Genova P, Memeo R, Brunetti F

Literature review: Genova P

Writing: Genova P

Revision: Genova P, Memeo R, Brunetti F

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Gender disparities in weight loss surgery

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Abstract

Obesity is a growing epidemic affecting more than one third of the United States' population. It has detrimental effects on an individual's health and is associated with myriad negative outcomes including increased mortality. It also poses a substantial financial burden on the healthcare system. Weight loss surgery is an effective way of treating obesity with tremendous positive outcomes. Most patients who undergo bariatric surgery lose a significant amount of weight, reverse most of their comorbidities, and enjoy an improved quality of life. However, fewer than one percent of patients eligible for bariatric surgery actually undergo treatment. Furthermore, there exists a considerable gender disparity, with women comprising 80% of those patients who undergo bariatric surgery, despite equal obesity rates across genders. Many barriers exist between obese patients and weight loss surgery including misconceptions among patients and primary care providers regarding the perceived risk of surgery. This is in addition to numerous other psychosocial and cultural factors that may have contributed to and precipitated the existing gender imbalance. This review aims to highlight barriers to patients undergoing bariatric surgery and examine factors leading to the gender disparity that exists.

Keywords: Bariatric surgery, weight loss, gender disparity, obesity

INTRODUCTION

Obesity is a growing epidemic in the United States, affecting over one third of the population^[1,2]. Numerous adverse health outcomes are associated with obesity, including type 2 diabetes, obstructive sleep apnea and cardiovascular disease, resulting in disability and substantial health care costs^[3]. It is estimated that in 2013 obesity cost the healthcare system \$116 billion, of which \$69 billion were attributed to severe obesity^[4]. In addition, obesity has been linked with a shortened life expectancy^[5], with approximately 122,000 deaths in the U.S. per year associated with obesity^[6]. Weight loss surgery is often a last resort for patients, but may be



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the only sustainable option for improved health outcomes, resulting in more than 50% loss of excess body weight at 5 years postoperatively, significant improvements in chronic comorbid conditions, and improved life expectancy^[6-8].

Bariatric surgery is among the most common abdominal operation performed in the United States, with approximately 228,000 cases performed in 2017^[9,10]. Minimally invasive laparoscopic weight loss procedures now account for over 90% of bariatric surgeries performed, with perioperative mortality rates declining to less than 0.1% over the past decade^[3,9]. Patients referred for surgical evaluation at a bariatric program are typically seen by a multidisciplinary care team including a bariatric nurse, internist, psychologist or social worker, nutritionist, and surgeon to determine eligibility and optimize postoperative outcomes in selected patients^[11].

Despite the tremendous benefits and well-documented safety of bariatric surgery, currently fewer than 1% of Americans medically eligible for weight loss surgery actually undergo treatment^[12,13]. Referral patterns by primary care providers (PCP) seem to be the biggest barrier to undergoing bariatric surgery. A recent meta-analysis suggested that patient and PCP concerns regarding complications and potential death from surgery were notable barriers to pursuing weight loss surgery^[13]. However, providers who were more knowledgeable about bariatric surgery were more likely to refer their patients for consideration^[13]. Additionally, Wee *et al.*^[14] reported that a recommendation by a PCP increased the likelihood that a patient would consider weight loss surgery by five times.

While the prevalence of obesity among men and women is similar in the general population, a substantial gender disparity has persisted over the past decade in bariatric surgery, with women comprising over 80% of patients undergoing weight loss surgery^[2,15]. In addition to socioeconomic factors that influence access to bariatric surgical care, the complex interplay among gender, psychosocial, and cultural factors may pose an additional challenge to ensuring that all eligible patients, regardless of gender, are receptive to the option of weight loss surgery and have realistic expectations of outcomes after treatment.

We evaluated recent studies assessing demographic trends in bariatric surgery, as well as studies examining utilization and outcomes with a focus on gender disparities. We further evaluated and selected current literature based on the inclusion of themes relevant to gender-based differences in bariatric surgery care, including patient and provider perceptions of weight-loss surgery, provider referral patterns, and patient selection. We then sought to elucidate the sex-based differences in clinical and psychosocial outcomes after bariatric surgery. Our aim here is to highlight factors associated with the gender imbalance in the surgical treatment of obesity, review outcomes after surgery, and explore the critical opportunity for further collaboration between bariatric surgical specialists and PCPs to more effectively address gender-based disparities in obesity treatment.

BARIATRIC SURGERY ELIGIBILITY AND UTILIZATION

The National Institutes of Health (NIH) obesity management guidelines recommend bariatric weight loss surgery as a treatment for morbidly obese patients with a BMI > 40 kg/m² or a BMI of 35-40 kg/m² and obesity-related comorbidities^[3,16]. Although obesity rates were once higher in female patients compared to male patients, these differences have gradually disappeared since the early 2000s^[17]. A review of the 2009-2010 National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of obesity was similar among adult male and female patients with a prevalence of 35.5% and 35.8%, respectively^[18]. This suggests that the obesity rate may be climbing more rapidly in male than in female patients. However, the utilization of bariatric surgery is outstandingly lower among eligible men than women. In an analysis of the National Hospital Discharge Survey, which provides data on patients who have undergone bariatric surgery from 1999 to 2010, Mainous *et al.*^[1] found that, across racial groups, a significantly higher

proportion of eligible women received bariatric surgery compared to eligible men. Another review of the Nationwide Inpatient Sample database from 2002 to 2011 showed similar results. Of the 810,999 patients who underwent bariatric surgery over that 10-year period, only 19.3% were men^[19]. These data imply that there is a gender-based disparity in the utilization of weight loss surgery among eligible patients.

Several studies demonstrate that a higher proportion of female bariatric surgery patients are younger (less than 45 years old) compared to their male surgical counterparts^[1,15]. The increased proportion of younger women undergoing weight loss surgery may be due to strong cultural and social pressures to seek a thin body weight ideal resulting in higher patient request and referral for surgical evaluation^[14,15,20]. Indeed, over 70% of referrals to bariatric surgical programs in the published literature are female and about half of the referrals are initiated by patients rather than by primary care physicians or other referring doctors^[20-22]. These patterns suggest that patient-driven requests for evaluation at the primary care level are relevant to the gender imbalance seen among patients ultimately selected for surgical treatment. Additionally, bariatric surgery utilization by young women may reflect fertility issues as a result of obesity, resulting in surgical treatment to improve chances of a successful pregnancy and to reduce the risks of pregnancy-related complications^[23,24].

In contrast, social, cultural, and reproductive pressures to address weight perhaps provide less of an impetus for morbidly obese men to pursue surgical treatment earlier. Male patients typically present for surgery at an older age and with more comorbidities, including more than double the prevalence of coronary artery disease and history of myocardial infarction compared to morbidly obese women^[1,15]. This delayed presentation for surgical treatment among men increases their risk of morbidity, disability, and mortality. In addition, among patients who initially attend a bariatric program for consideration of surgery, men are significantly more likely than women to drop out of the process without undergoing surgery (OR = 0.527, $P < 0.001$)^[20].

Although obesity rates are equal among genders, men are significantly less likely to be referred or undergo bariatric surgery. Understanding the gender-based differences in referral, program attrition, and utilization of bariatric surgical treatment are relevant to ensuring that high risk patients are adequately identified before potentially disabling and life-threatening comorbidities develop.

GENDER-SPECIFIC WEIGHT PERCEPTIONS AND QUALITY OF LIFE

The gender disparity among bariatric surgical patients may in part be explained by gender-based differences in perceptions of body weight and obesity-related quality of life, which may have an impact on the motivation to request evaluation for surgery, as well as follow through with treatment. In a study by Tsai *et al.*^[25], data from NHANES were used to evaluate gender-specific weight perception across increasing BMI. Compared with their female counterparts, overweight and obese men were less likely to have an accurate weight perception, weight dissatisfaction, and attempted weight loss. Some studies have found more pronounced gender-based difference among obese blacks compared to whites, suggesting that ethnicity and culture influence perceptions of ideal body weight^[1].

In a study of over 330 patients with a BMI of 35 kg/m² or higher recruited from primary care practices, Wee *et al.*^[14] assessed the relationship among obesity, perception of body weight, and patient quality of life via the Impact of Weight on Quality of Life-lite (IWQOL-lite) survey, which was specifically designed for use with obese individuals. IWQOL-lite examines domains including physical function, public distress, self-esteem, sexual life, and work. In this patient sample, women were disproportionately negatively affected by their weight compared to men, with statistically significantly lower Quality of Life (QOL) overall scores, as well as in the specific domains of weight-related social stigma, self-esteem, public distress, and physical functioning.

White *et al.*^[26] identified similar gendered patterns in obesity-related QOL using IWQOL-lite in a study of 512 individuals actively undergoing evaluation for bariatric surgery. Despite having the lowest overall

BMI levels within the sample, white women had the most impaired QOL, and African American men had the least impairment. Within specific domains, black men (67%) and white men (63%) were more likely to report physical functioning deficits, compared to black women (51%) and white women (46%). Obesity related sexual limitations were identified as the most commonly reported impairment among both black women (35%) and white women (24%) compared to only 11% of white men and no black men.

These studies suggest that psychosocial distress associated with obesity is more strongly experienced by women and perhaps may explain part of the trend to presentation at a younger age, when social and cultural pressures are strongest. As Tsai *et al.*^[25] suggested, culturally accepted ideal male body types may permit a heavier weight without social detriment or decreased sense of self-esteem. However, it appears that detriments to physical agency brought on by morbid obesity and its comorbidities do have an impact on QOL for men and may be an important motivation for seeking treatment. Thus, a vital step in counseling patients for weight loss and consideration of bariatric surgery may involve helping patients identify morbid obesity as a serious health problem through its impact on aspects of day-to-day life that matter most to the individual, with sensitivity to gendered patterns of self-perception and coping with obesity-related impairments.

GENDER-SPECIFIC PERCEPTIONS OF WEIGHT LOSS SURGERY

In addition to gender-based differences in coping with morbid obesity and quality of life concerns, perceptions of bariatric surgery itself and motivations to pursue surgery may differ between men and women. Among 325 primary care patients with a BMI of 35 kg/m² or higher, Wee *et al.*^[27] explored demographic and quality of life factors affecting patient consideration of bariatric surgery and found that the majority of patients were aware of weight loss surgery, and overall 37% had ever seriously considered undergoing surgical treatment. Broken down by gender, 40% of women had ever considered surgery compared to 22% of men ($P < 0.05$). Only 35% of this patient cohort reported ever having received information about surgical weight loss options from a provider, with no gender differences. However, women were more likely to have received a physician recommendation for surgery compared to men (22% vs. 14%, $P < 0.05$). This is interesting given that nearly half of patients responded that they would seriously consider weight loss surgery if recommended by their provider, and this held true for both men and women. With regards to the other half, the perception of weight loss surgery as “too risky” was the most commonly reported deterrent to considering bariatric surgery across gender and ethnicity groups^[27]. Both patient perceptions of risk associated with weight loss surgery as well as physician behaviors related to patient education and treatment recommendations influence individual and gender-specific consideration of surgical treatment options.

Patient motivations for pursuing weight loss surgery have been shown to differ by gender, echoing differences observed regarding self-perception of body weight and associated impairments in quality of life. In an Australian study of 208 participants approximately one year postoperatively after laparoscopic adjustable band placement, patients who reported distress related to appearance as a primary motivation to pursue weight loss surgery were more likely to have a lower presenting BMI and to be female ($P = 0.03$ and $P < 0.001$, respectively)^[28]. Additionally, patients who were motivated primarily by medical conditions were more likely to be men ($P = 0.007$), to be older, and to have hypertension or diabetes. Similarly, in a majority women (95%) United States survey study of 44 patients evaluated for bariatric surgery, 84% of participants noted psychosocial concerns as an extremely important motivating factor for surgery, although health-related reasons were also ranked by most as equally critical^[29]. Patients expressed high expectations for sustained weight improvement on the order of about 80% of excess weight loss with surgical intervention. The authors noted that this degree of weight loss cannot always be achieved postoperatively and suggested that it is critical for patients to have more accurate weight loss expectations in order to achieve sustained satisfaction and improved outcomes after surgery.

As men are underrepresented in the majority of bariatric surgical studies, Natvik *et al.*^[30] conducted a qualitative focus group study including 13 men who had previously undergone bariatric surgery to better understand their experience with surgical treatment. The men being interviewed reported that their initial misconceptions regarding weight loss surgery involved associating the treatment with “vanity, which they regard as valueless and shallow and did not relate to”^[30]. Prior to surgery, many men in the group had tried other weight loss options on their own, expressing that autonomy and independence were critical to addressing weight problems. The majority of men reported having suffered an acute illness such as stroke or heart attack, which brought up themes of powerlessness and an emerging realization of needing help for obesity, which they began to understand as a serious illness only after experiencing weight-related complications.

In this small cohort, evaluation for surgical weight loss treatment was frequently initiated by a healthcare professional or family member rather than by the men themselves. However, some men reported that the pursuit of weight loss surgery revived a sense of self-efficacy, which facilitated a commitment to treatment. While clearly a small study with limited generalizability and potential recall bias, this qualitative exploration of men’s perceptions of bariatric surgery demonstrated that misconceptions of the purpose of bariatric surgery, that it is for body image rather than health, may be a significant barrier to appropriate treatment for men. The findings suggest that effective counseling of obese patients requires a gendered understanding of how patients individually relate their bodies and how that relationship is connected to what individuals value most in terms of physical and psychological health, as well as with respect to autonomy and personal agency.

KNOWLEDGE GAP, PROVIDER REFERRAL, AND PATIENT SELECTION PATTERNS

Although patients’ perception and motivation to pursue weight loss surgery play a major role in access to bariatric surgery, the knowledge gap and increased perceived risk on behalf of providers and patients pose significant barriers between morbidly obese patients and surgical treatments. In a survey study of over 470 physicians, Avidor *et al.*^[21] reported that, among primary care physicians as well as other specialists in obstetrics and gynecology, cardiology, and endocrinology, most physicians had only moderate familiarity with the NIH morbid obesity management guidelines, safety of surgical options, and the long-term impact of surgery on weight and comorbidities. Additionally, the dominant reason for physician non-referral was provider lack of knowledge of a local bariatric surgeon, suggesting that surgical specialists need to improve outreach efforts and to expand surgical resources to underrepresented regions. Additionally, nearly half of gynecologists were unaware of published studies on the effects of bariatric surgery on restoring fertility in morbidly obese females. Furthermore, up to 35% of primary care practitioners surveyed have reported feeling unprepared to provide long-term medical care for post-surgical patients and less than half felt competent to manage medical complications of bariatric surgery^[22].

Additionally, perceptions of weight loss surgery as carrying increased risk further hinder access across genders. Funk *et al.*^[31] conducted focus groups with 16 PCPs in Wisconsin to better elucidate their perception of obesity and weight loss surgery. Interestingly, providers were primarily focused on obesity being a risk factor for disease instead of considering it a disease in and of itself. This is despite the American Medical Association resolution in 2013 characterizing obesity as a disease. Additionally, decision making by PCPs often under-prioritized treatment for obesity and over-emphasized risk of surgery. This study outlined several factors including PCPs wanting to “do no harm”, and questioning the effectiveness of weight loss surgery as reasons for not referring patients^[32]. However, the data argue against this, and repeatedly bariatric surgery has been shown to be equally safe as, and in some cases more safe than, other well accepted surgical procedures. Aminian *et al.*^[33] compared the safety of the laparoscopic Roux-en-Y gastric bypass (LRYGB) to seven other procedures in diabetic patients using NSQIP data between 2007 and 2012. The complication rate of LRYGB (3.4%) was comparable to that of laparoscopic cholecystectomy (3.7%) and laparoscopic hysterectomy (3.5%), and significantly lower than that of total knee arthroplasty

(16.7%). This is interesting since obesity is a major risk factor for osteoarthritis, which in turn is the most common indication for a knee replacement. Similarly, LRYGB had a lower mortality rate than laparoscopic cholecystectomy and appendectomy (0.3% vs. 0.7% and 0.5%, respectively). Future partnerships between bariatric surgeons and PCPs are crucial to increase knowledge about the safety of weight loss surgery.

Although referral patterns seem to be a larger barrier for access to weight loss surgery, patient selection by bariatric surgeons may also be implicated in the gender disparity. In a national survey study by Santry *et al.*^[34], patterns of patient selection among 820 U.S. bariatric surgical specialists was examined using clinical patient vignettes. In all BMI and comorbidity subgroups that met current NIH clinical guidelines for surgery, patient gender did not influence patient selection. This insinuates that the overrepresentation of women undergoing bariatric surgery likely occurs prior to evaluation by a bariatric surgeon and is either related to referral patterns or patient preference. However, the study did find that gender had an impact on patient selection only for the subset of patients who did not meet NIH BMI and comorbidity criteria. In this subset, men had a 67% decreased odds of selection for surgery. While the majority of patients who do not meet NIH criteria are often self-referred and appropriately excluded from surgical evaluation^[11], the findings from the Santry *et al.*^[34] study suggest that some surgeons may be influenced by social and cultural pressures on women to achieve body image ideals. Bariatric surgery for this subset of patients, however, likely does not completely account for the gender disparity across all bariatric surgical patients, the majority of which meet NIH criteria.

SEX-BASED OUTCOMES AFTER BARIATRIC SURGERY

Similar to the knowledge gap about the safety of weight loss surgery, differential referral for and utilization of bariatric surgery by men and women may also be founded in a lack of knowledge, on the part of both providers and patients, surrounding the effectiveness of weight loss and health risk reduction with surgery. Kennedy-Dalby *et al.*^[35] sought to compare sex-based outcomes in an observational cohort analysis of 79 men matched to 79 women for age, BMI, bariatric procedure, and comorbidities including type 2 diabetes and obstructive sleep apnea. At 24 months postoperatively, significant reductions in excess BMI loss were identified for both women and men (72.9% and 65.8%, respectively). Both groups demonstrated significant reductions in hypertension, glycosylated hemoglobin, and cholesterol without significant differences by gender. Additionally, 77.5% of men and 90.0% of women with obstructive sleep apnea discontinued continuous positive airway pressure use. These findings support bariatric surgery as an effective weight loss intervention with significant improvement in metabolic and functional outcomes for both men and women.

Weight loss surgery has also been shown to have positive effects on sexual functioning, fertility, and pregnancy outcomes in women. In a prospective cohort study of 106 women who underwent bariatric surgery, Sarwer *et al.*^[36] reported that, within the first two postoperative years, women report significant improvements in overall sexual functioning as well as in specific domains related to arousal, lubrication, desire, and satisfaction. These observations correlated with significant improvements in levels of sex hormones as well as in important shifts across quality of life measures, including improvement in depressive symptoms, self-esteem, and overall emotional and physical functioning. Weight loss after bariatric surgery is associated with improvement in conditions such as polycystic ovarian syndrome, anovulation, and irregular menses, leading to improvement in fertility rates as well as reductions in pregnancy loss and maternal pregnancy complications such as gestational diabetes and preeclampsia^[24].

Among men pursuing bariatric surgery, 36% report sexual dissatisfaction associated with erectile dysfunction^[23]. Additionally, elevated BMI has been associated with impairments in semen characteristics and reduced levels of reproductive hormones potentially affecting male fertility^[37]. In a study of 97 men undergoing gastric bypass, participants reported significant improvement in sexual function based on the Brief Male Sexual Function Inventory score before and after surgery. There was improvement in all

categories, including sexual drive (3.9 ± 0.3 to 5.3 ± 0.3), erectile function (6.4 ± 0.5 to 8.9 ± 0.5), ejaculatory function (4.9 ± 0.4 to 6.3 ± 0.4), problem assessment (7.4 ± 0.5 to 9.6 ± 0.5), and sexual satisfaction (1.6 ± 0.2 to 2.3 ± 0.2 ; all $P < 0.01$)^[38]. Other studies have also demonstrated improvements in sexual quality of life after bariatric surgery, as well as favorable reproductive hormonal alterations in men^[39,40]. The biologic (improvement in sex hormone levels) and gender-related aspects of weight loss (in part body image-related) likely work in symbiosis to create renewed vitality and a positive sense of identity for both men and women.

Vegel *et al.*^[41] further examined QOL outcomes after bariatric surgery at a single institution using the Moorehead-Ardelt Quality of Life Questionnaire II (MAQoLII). In total, 209 patients underwent bariatric surgery from 2010 to 2012, with 79% being women. There was a significant improvement in scores both overall and across each category of QOL measures at one-year postoperatively compared to preoperatively, including in physical functioning, self-esteem, and sexual function. Gender was not associated with a change in outcome. In a prospective study of 32 men who underwent bariatric surgery conducted by Sarwer *et al.*^[42], participants reported significant improvements in physical quality of life measures, weight-related quality of life, and body image. All this proposes that, although men may not initially view the downsides of obesity on their health and functional capacity, bariatric surgery seems to significantly improve quality of life measures in both genders equally.

CONCLUSION

Bariatric surgery has evolved to become a safe and effective treatment for morbid obesity with favorable outcomes for both women and men. However, significant barriers exist between morbidly obese patients and bariatric surgical treatment, and, although these barriers exist for both men and women, there is clearly a gender disparity with far fewer eligible men receiving appropriate treatment. Thus, greater efforts are needed to improve overall access to surgical care and narrow the gender gap. This can only be accomplished through collaborations between bariatric surgical specialists and primary care providers to ensure that eligible patients receive meaningful education about the risks and benefits of surgery with attention to gendered concerns and expectations. Primary care providers, who continue to be the most important source of patient referral^[11], are in a frontline position to identify patients who may benefit from surgery and to understand patients' health-related and social values, working closely with those who may be reticent to consider bariatric surgery and less likely to independently express interest in a surgical evaluation when appropriate. Individualized multidisciplinary support remains vital throughout both the evaluation and treatment process to ensure commitment to surgery and long-term success, as surgical weight loss can truly result in profound positive changes across all aspects of life.

DECLARATIONS

Authors' contributions

Conceived the original idea: Hachey K

Contributed to the drafting of the manuscript and critical revisions: Aly S, Hachey K, Pernar LIM

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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Original Article

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Robotic lateral heller myotomy without fundoplication for achalasia

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Abstract

Aim: Laparoscopic anterior esophageal myotomy with a Dor anterior fundoplication is the most commonly performed surgical myotomy procedure. A lateral esophageal myotomy without an antireflux procedure performed through a left thoracotomy has been associated with the lowest rate of postoperative gastroesophageal reflux and the highest rate for relief of dysphagia. The surgical robot allows for the lateral myotomy procedure to be performed by laparoscopy rather than thoracotomy. We studied our experience with Robotic Lateral Heller Myotomy Without Fundoplication (RLHM) for achalasia.

Methods: A retrospective review was conducted of the patients with achalasia who underwent RLHM. All patients completed a subjective dysphagia score questionnaire, received an Eckardt Score, and underwent manometry and pH testing preoperatively, as well as at 6 and 12 months following the myotomy procedure.

Results: Forty-eight patients underwent RLHM. The median operating room time was 85 min (range 60-132 min). There was no conversion to a laparotomy. Median hospitalization was 2 days (range 2-3 days). There were no mucosal perforations, complications, or deaths. Following RLHM, the Lower Esophageal pressure decreased from 35 mmHg (range 18-120 mmHg) to 13.2 mmHg (range 9.8-16.6 mmHg) ($P < 0.0001$). The length of the Lower Esophageal high-pressure zone decreased from 5.5 cm (range 4-9 cm) to 2.2 cm (range 1.5-2.8 cm) ($P < 0.0001$). Two patients (2/48) (4.2%) had pathologic gastroesophageal reflux. The median acid exposure in all patients was 0.4% (range 0%-17.8%), and the median Demeester score was 7.5 (range 2-125). The Eckardt score decreased from 6.3 ± 1.8 to 0.8 ± 1.8 at 1 month ($P < 0.0001$), and 0.8 ± 1.1 at 12 months ($P < 0.0001$).

Conclusion: RLHM is associated with excellent relief of dysphagia and a low incidence of new gastroesophageal reflux.



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Keywords: Achalasia, robotic, heller myotomy, laparoscopic, eckhardt score

INTRODUCTION

Achalasia is characterized by abnormal relaxation of the lower esophageal muscle and absence of progressive peristalsis in the body of the esophagus^[1]. In patients with achalasia, histopathologic studies of the lower esophagus have shown depletion of the ganglion cells and inflammation of the myenteric plexus^[2-3]. Since the function of the lower esophageal myenteric plexus cannot be restored, presently, the treatment of achalasia is palliative. The therapeutic options include medical therapy, botulinum toxin injections, pneumatic dilation, and distal esophageal myotomy by laparoscopy or endoscopy.

Although laparoscopic anterior esophageal myotomy with a Dor anterior fundoplication is the most commonly performed surgical myotomy procedure, several controversies persist, including the ideal operative approach, anterior *vs.* lateral esophageal myotomy, the extent of esophageal myotomy, and the need for the addition of an antireflux procedure.

Ellis *et al.*^[4] reported that, after a lateral esophageal myotomy without an antireflux procedure performed through a left thoracotomy, there was 96% relief of dysphagia and 3.5% rate of post myotomy gastroesophageal reflux. An anterior myotomy is thought to divide the gastroesophageal valve at its midpoint, necessitating an antireflux procedure. However, by performing the myotomy laterally and preserving the antireflux barrier, a fundoplication may be unnecessary. On the other hand, a lateral myotomy by thoracoscopy has been associated with high rates of post-myotomy reflux^[5]. These results have been attributed to the shortcomings of conventional videoendoscopic visualization and instruments. By virtue of high definition magnified 3D visualization and precise instrument maneuverability in a small space, it has been reasoned that a surgical robot can enable the lateral myotomy procedure to be performed by laparoscopy. We studied our experience with robotic laparoscopic lateral Heller myotomy without an antireflux procedure for achalasia (RLHM).

METHODS

A retrospective review was conducted of the patients with achalasia who underwent RLHM. Diagnosis of achalasia was made by esophagogram, endoscopy, and manometry. Patients who had previously undergone a myotomy or had a hiatal hernia were excluded from this study. Patients who had undergone a previous myotomy underwent redo myotomy by left thoracotomy, and patients with a hiatal hernia underwent an anterior myotomy with repair of the hiatal hernia and Dor fundoplication. All patients completed a subjective dysphagia score questionnaire, received an Eckardt score, and underwent manometry and pH testing preoperatively. The dysphagia score, manometry, and pH testing were repeated at 6 months following the myotomy procedure. The validated dysphagia score instrument scores subjective severity and frequency of dysphagia on a scale from 0 to 5 with a total possible Score of 0-10 for each individual^[6]. The dysphagia score is presented as median and range. The Eckardt achalasia scoring instrument scores dysphagia, regurgitation, retrosternal pain, and weight loss from 0 to 3 with a total possible score of 0-12 for each individual^[7]. In addition, the Eckardt score was tabulated at 1 and 12 months after RLHM. The Eckhardt score is presented as mean \pm SE. Failure of myotomy was defined as an Eckhardt score of ≥ 3 .

The study was reviewed and determined to be exempt from institutional review board approval under 45 CFR 46.101 (b).

Surgical technique

The procedure is performed on a laparoscopic platform [Figure 1]. Preoperative upper gastrointestinal endoscopy is performed and the gastroesophageal junction is examined by the retroflexed endoscope.

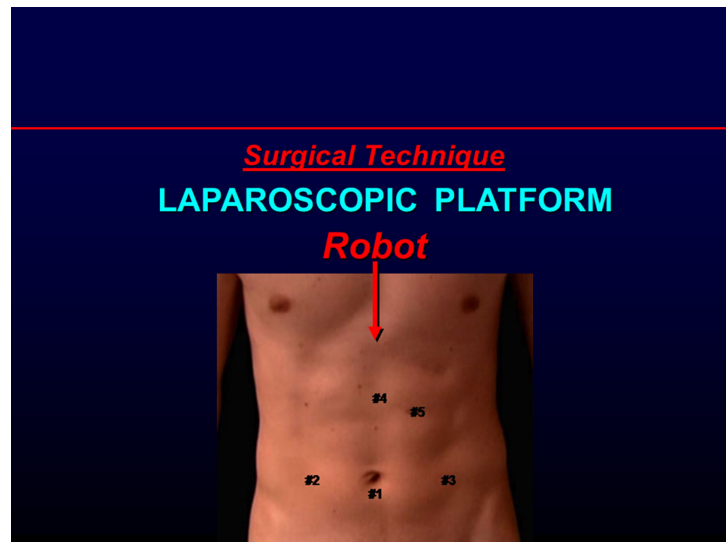


Figure 1. Positioning the robot and trocars for the robotic approach



Figure 2. Positioning the robot for the robotic laparoscopic approach

Two Laparoscopic CO₂ insufflators are used. Port 1 (Camera Port) is placed inferior to the umbilicus. Pneumoperitoneum is created. The table is placed in a steep reverse Trendelenberg position. Port 2 is placed in the right paraumbilical region at the right mammary line. Port 3 is placed in the left paraumbilical region in the left mammary line. An Endo-Paddle paddle retractor (Medtronic, Norwalk, Conn.) is introduced through Port 2 and used to place upward traction on the left lobe of the liver. Port 4 is placed in the subcostal region halfway between the umbilicus and the xiphoid just to the left of the midline. This port is aligned with the right limb of the right crus of the diaphragm. Port 5 is placed in the subcostal region two finger-breaths to the left and caudad to Port 4. Port 5 is aligned with the left limb of the right crus of the diaphragm.

The surgical robot (Da Vinci Si, Intuitive Surgical, Sunnyvale, CA) is docked using the “side docking” technique [Figure 2]. A 30-degree down-viewing robotic binocular camera is used, which is introduced through Port 1. The right robotic arm with a hook cautery instrument is introduced through Port 3. The



Figure 3. Laparoscopic view of the completed lateral esophageal myotomy prior to the re-approximation of the left limb of the esophageal crus

left robotic arm with a Debaquey grasper instrument is introduced through Port 2. The entire dissection uses electrocautery and meticulous hemostasis. An Endo-Paddle Retract Retractor (Covidian, Norwalk, Conn, USA) is introduced through Port 5 by the assistant and is used to provide appropriate counter traction and exposure at the esophagogastric junction.

The left limb of the esophageal crus is identified, and the muscle is divided perpendicular to the direction of the fibers for half the width of the crus. Care is taken not to enter the pleura, which resides just under the crus. The left limb is not transected completely. This allows for partial retraction of the muscle away from the lateral aspect of the gastroesophageal junction while at the same time facilitating repair of the left limb at the end of the procedure. The hook cautery is set at 30 cut/30 coagulation with blend setting. The stomach is retracted inferiorly, thereby straightening the gastroesophageal (GE) junction. Care is taken to stay on the left lateral aspect of the gastroesophageal valve. Theoretically, by preserving the gastroesophageal valve and the phreno-esophageal ligament, the antireflux mechanism is kept intact. The muscle of the esophagus is divided to the level of the mucosa. The hook cautery then completes the myotomy approximately 2 cm onto the cardia of the stomach. Myotomy is discontinued when the submucosal vascular plexus of the stomach wall is visualized [Figure 3]. The myotomy is extended cephalad on the esophagus to the level of the pleura. The total length of the myotomy is approximately 6 cm.

At this point, an assistant who is positioned at the head of the patient advances the gastroscope past the GE junction into the stomach. The ease of movement of the gastroscope into the stomach and the lack of resistance further confirms the complete division of the esophageal muscles at the GE junction. Furthermore, the gastroscope is retroflexed to view the GE junction from a caudad to cephalad direction [Figure 4]. Observation of the trans-illuminated mucosa of the proximal portion of the gastric cardia from the light of the robotic camera serves as the final confirmation for the completion of the esophageal myotomy. The retroflexed view further confirms that the myotomy is lateral to the gastroesophageal valve. Following the completion of the myotomy, the area is filled with saline and the gastroscope is used to insufflate air into the stomach and esophagus in order to rule out any mucosal perforation.

Following a satisfactory myotomy, the partially transected left limb of the esophageal crus is reapproximated with two O-Ethibond sutures (Ethicon, Inc. Somerville, NJ) with 2-cm square absorbable pledgets cut from Vicryl mesh (Ethicon, Inc. Somerville, NJ).

A video of the procedure can be accessed at <https://www.youtube.com/watch?v=WUEuHSiodY&feature=youtu.be>.

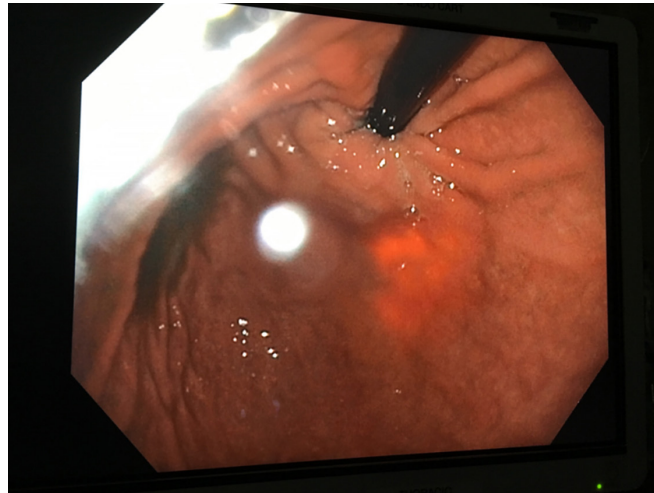


Figure 4. Retroflexed endoscopic view of the intact gastroesophageal valve and trans-illuminated lateral esophageal myotomy

RESULTS

Forty-eight patients underwent RLHM. There were 25 men and 23 women with a mean age of 48 ± 21 years. Median OR time was 85 min (range 60-132 min). There was no conversion to a laparotomy.

Median hospitalization was 2 days (range 2-3 days). There were no mucosal perforations, complications, or deaths. Manometry data are shown in [Table 1](#).

Following RLHM, the Lower esophageal (LES) Pressure decreased from 35 mmHg (range 18-120 mmHg) to 13.2 mmHg (range 9.8-16.6 mmHg) ($P < 0.0001$). The length of the LES high-pressure zone decreased from 5.5 cm (range 4-9 cm) to 2.2 cm (range 1.5-2.8 cm) ($P < 0.0001$) [[Table 2](#)].

Following RLHM, based on the DeMeester score, two patients (4.2%) had pathologic gastroesophageal reflux. Median acid exposure in all patients was 0.4% (range 0%-17.8%), and the median DeMeester score was 7.5 (range 2-125).

Following RLHM, the dysphagia score decreased from 9 (range 8-10) to 1 (range 0-1) ($P = 0.01$) [[Table 3](#)].

Eckardt scores are shown in [Table 4](#). Following RLHM, the Eckardt score decreased from 6.3 ± 1.8 to 0.8 ± 1.8 ($P < 0.0001$) at 1 month and 0.8 ± 1.1 at 12 months ($P < 0.0001$). Postoperatively, all patients had an Eckhardt score of less than 3.

DISCUSSION

The surgical therapy of achalasia has evolved with a better understanding of the disease process, the anatomy of the GE junction, and the nature of the “antireflux barrier”, as well as advances in technology.

Over the years, surgical therapy for achalasia has been controversial. The controversy has centered on the ideal operative approach, the extent of esophageal myotomy, and the need for the addition of an antireflux procedure. With minor changes, presently, the same controversies continue.

A better understanding of the antireflux barrier has been crucial in understanding the reasons for the controversies. The antireflux barrier, which corresponds to the high-pressure zone on esophageal manometry, seems to be the result of the following:

Table 1. Comparison of preoperative and postoperative LES high-pressure zone pressure (6 months)

Postoperative LES pressure median (range)		
Preop	Postop	P value
35 mmHg (18-120)	13.2 mmHg (9.8-16.6)	< 0.0001

LES: lower esophageal

Table 2. Comparison of preoperative and postoperative LES high-pressure zone length (6 months)

Length of LES high-pressure zone median (range)		
Preop	Postop	P value
5.5 cm (4-9)	2.2 cm (1.5-2.8)	< 0.0001

LES: lower esophageal

Table 3. Comparison of preoperative and postoperative dysphagia score (6 months)

Dysphagia score median (range)		
Preop	Postop	P value
9 (8-10)	1 (0-1)	< 0.01

Table 4. Comparison of preoperative and postoperative (12 months) Eckhardt score

Eckhardt score mean \pm SE		
Preop	Postop	P value
6.3 \pm 1.8	0.8 \pm 1.8	< 0.0001

- (1) The anterior and lateral intussusception of the esophagus into the stomach, extending 270 degrees from the right limb of the right crus to the left limb of the right crus of the diaphragm.
- (2) The crural sling exerts pressure in an anterior to posterior direction onto the GE junction and creates a slight angulation. This angulation at the GE junction serves to hold the intussuscepted esophagus in place and provides a slight resistance to reflux at the GE junction.
- (3) The entire “antireflux” mechanism is held in place by the phreno-esophageal ligament and the tissues at the esophageal hiatus.
- (4) Disruption of the esophageal hiatus, either with a hiatal hernia or at the time of surgical dissection, leads to the straightening of the GE junction, reduction of the anterior esophageal intussusception, and the creation of gastroesophageal reflux.

Prior to the advent of the laparoscopic approach to achalasia, the most commonly performed procedure for this disease was the transthoracic modified Heller myotomy with or without an antireflux procedure. The transthoracic approach was preferred to the transabdominal approach due to the technical difficulties of exposing the gastroesophageal junction and the distal esophagus by an open abdominal procedure. Ellis *et al.*^[4] advocated transthoracic esophageal myotomy without an antireflux procedure with very low rates of postoperative reflux^[8,9]. The advent of laparoscopy obviated the morbidity of a thoracotomy, and laparoscopic Heller myotomy with an anterior Dor fundoplication became one of the more frequently adopted surgical techniques for treating esophageal achalasia^[10-18].

In 1991, Shimi *et al.*^[19] reported the first laparoscopic experience for Heller myotomy. In one series of 133 patients who had undergone laparoscopic myotomy with a partial fundoplication, Patti *et al.*^[20] reported 11% persistent dysphagia, 17% new gastroesophageal reflux, and 5% mucosal perforations that were amenable to laparoscopic closure. Invariably, all series reporting the laparoscopic approach to Heller myotomy have shown excellent relief of dysphagia. The majority of difficulties with the laparoscopic approach have been related to reflux and the technical aspects of the fundoplication. In a series of 69

patients undergoing laparoscopic myotomy and fundoplication for achalasia, Finley *et al.*^[18] reported a median operative time of 1.9 h, one mucosal perforation that was amenable to laparoscopic repair, 96% patient satisfaction for relief of dysphagia, and a 9% rate of new postoperative gastroesophageal reflux.

A generous anterior myotomy including onto the gastric cardia has been advocated to prevent incomplete myotomy presenting as residual achalasia. To prevent postoperative reflux, a fundoplication should be performed as well. The fundoplication has also been demonstrated to prevent the formation of a mucosal diverticulum following myotomy, a condition which may have added to the problem of chronic dysphagia in these patients with compromised esophageal dysmotility^[18].

On the other hand, the surgeons who have advocated myotomy without an antireflux procedure, most notably Ellis *et al.*^[4], have emphasized that, in their experience, fundoplication recreates the resistance to esophageal emptying and that, depending on the degree of resistance, fundoplication can lead to progressive esophageal dilation and ultimately the same sequelae as with untreated achalasia. Furthermore, based on performing a lateral esophageal myotomy, these authors have asserted that, in their experience, if the esophageal myotomy is carried onto the cardia by up to 2 cm, an antireflux procedure is not required.

The present understanding of the gastroesophageal antireflux barrier has served to explain the different observations and the discrepancy in the experience of the proponents versus the opponents of an added antireflux procedure to the modified Heller myotomy. Based on this understanding, by nature of not disrupting the three-dimensional relationship at the esophageal hiatus and performing a very careful and limited myotomy, the surgeons who did not add an antireflux procedure were able to preserve the antireflux barrier and accomplish the goal of the myotomy without the need for an antireflux procedure. On the other hand, surgeons who opened the esophageal hiatus and performed an extensive dissection of the gastroesophageal junction, thus disrupting the normal antireflux barrier, needed to add an antireflux procedure to the myotomy in order to prevent postoperative reflux. It is important to note that, to visualize an adequate length of esophagus, a transabdominal approach invariably needs to disrupt the anatomy at the gastroesophageal junction and the antireflux barrier. Consequently, all transabdominal approaches to esophageal myotomy have required the addition of an antireflux procedure.

This is a retrospective review of patients who underwent a robotic laparoscopic esophageal myotomy without fundoplication. RLHM was performed without complications or mortality. There was significant decrease in the pressure and length of the lower esophageal high-pressure zone on manometry. The manometry data correlated with the significant decrease in the subjective dysphagia score. In addition, the objective Eckhardt scores decreased significantly and remained unchanged at 12 months following RLHM, signifying the long-term efficacy of the procedure. The rate of pathologic reflux following RLHM was very low. This finding is further evidence that RLHM preserves the gastroesophageal valve and does not require a fundoplication.

Long-term results of the laparoscopic anterior esophageal myotomy with an antireflux are excellent. Theoretically, by virtue of three-dimensional high definition magnification, and precise instrument maneuverability, the robotic laparoscopic approach may be associated with better outcomes for a procedure that requires exceptional surgical precision and visualization. In addition, the use of the surgical robot in performing a lateral esophageal myotomy may obviate the need for a fundoplication.

Given the excellent relief of dysphagia, and very low incidence of post myotomy gastroesophageal reflux, RLHM should be considered in patients with achalasia.

Study limitations

The following limitations of this study should be considered before drawing definitive conclusions. The study was limited to a small number of patients. In addition, the study was retrospective and represented a highly selected group of patients.

Undoubtedly, the use of robotic technology adds greater cost. If the results of this study are validated by a randomized prospective study, this shortcoming may be offset by the greater accuracy of dissection, the high rates of relief of dysphagia, and the low incidence of pathologic reflux associated with robotic lateral Heller myotomy without fundoplication for achalasia.

DECLARATIONS

Authors' contributions

Collection of data, planning and preparation of manuscript: Gharagozloo F, Atituzzman N, Atiquzzman B

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Technical Note

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Technical details of laparoscopic sleeve gastrectomy

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Abstract

Obesity is an expanding threat globally. Several surgical procedures have been developed to achieve the best outcomes in obesity. One of them is laparoscopic sleeve gastrectomy that was first applied in 1999 to initiate weight loss in overweight patients. Laparoscopic sleeve gastrectomy is a restrictive bariatric technique consisting of subtotal partial vertical gastrectomy with the preservation of the pylorus, and a gastric tube is created as a continuation of the esophagus along the lesser curvature with the resection of the fundus, corpus, and antrum. Although this technique is routinely-applied all over the world, the technical details are still controversial. This review aims to define the tips and tricks for the sleeve gastrectomy technique and discuss the controversial subjects in this technique.

Keywords: Bariatric Surgery, obesity, sleeve gastrectomy, technique

INTRODUCTION

Obesity is an expanding threat to the health of populations around the world. According to the National Health and Nutrition Examination Survey, the incidence of obesity was 39.8% in adults and 18.5% in youth in the United States between 2015 and 2016^[1].



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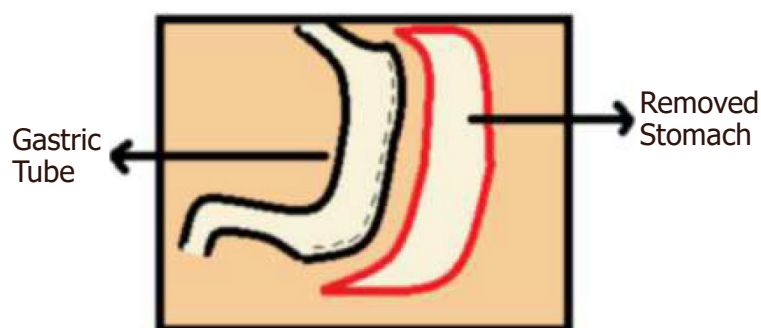


Figure 1. Demonstration of sleeve gastrectomy

Several endoscopic and surgical procedures have been advanced to achieve the best outcomes in obesity. Sleeve gastrectomy was first performed in 1990 as the first of a two-stage operation for biliopancreatic diversion with duodenal switch (BPD-DS)^[2]. Then, the first Laparoscopic Sleeve Gastrectomy (LSG) was applied in 1999. The original indication for sleeve gastrectomy was to initiate weight loss in super-obese patients [body mass index (BMI) > 60] to safely enter the second stage, BPD-DS. When these patients were followed, the excellent decrease in excess body weights was found, and in 2008 these findings were published with indications for LSG^[3]. When compared to other bariatric surgeries, sleeve gastrectomy is technically easier with relatively less morbidity and thus has become a commonly performed bariatric surgery as an obesity control modality. LSG has become the most common bariatric surgical procedure in recent years, and its short-term results have been reported to be effective and safe. ASMBS (American Society for Metabolic and Bariatric Surgery) considers sleeve gastrectomy (SG) to be an acceptable option for the primary bariatric procedure or as a first-stage procedure in high-risk patients. However, its effectiveness and long-term consequences are still being discussed^[4,5].

LSG is a restrictive bariatric technique consisting of subtotal partial vertical gastrectomy with the preservation of the pylorus. A gastric tube is created as a continuation of the esophagus along the lesser curvature with the resection of the fundus, corpus, and antrum [Figure 1]. Although LSG is claimed as a restrictive procedure, it has neuro-humoral effects that stimulate recovery in weight loss and concomitant diseases. Moreover, SG induces fast gastric emptying and causes early food transportation into the small bowel^[6]. Despite the established safety and efficacy of LSG, controversy still exists on optimal operative techniques. This review aims to present the LSG technique with controversial aspects in the light of our clinical experience and skills as a technical note.

SURGICAL TECHNIQUES

The operation is performed in reverse Trendelenburg position on an operating table with an angle of 30° and the surgeon takes position between the legs of the patient. Pneumo-peritoneum is performed with the Veress needle in the left upper quadrant. The five-trocar technique is used. The first (10-mm) trocar is placed at the upper abdomen 1-2 cm above the umbilicus as an optical trocar. A 5-mm trocar is inserted at the sub-xiphoid area for the Nathanson liver retractor [Figure 2]. A 15-mm trocar is introduced at the right upper quadrant and a 12-mm trocar is inserted at the left upper quadrant. Finally, a 5-mm trocar is introduced at the left subcostal anterior axillary line.

Firstly, the stomach is decompressed via a nasogastric tube by the anesthesiologist. Then, the omentum is released and ligated from the greater gastric curvature with the energy-based device continuing proximally into the esophagus and 2-4 cm proximal to the pylorus [Figure 3].

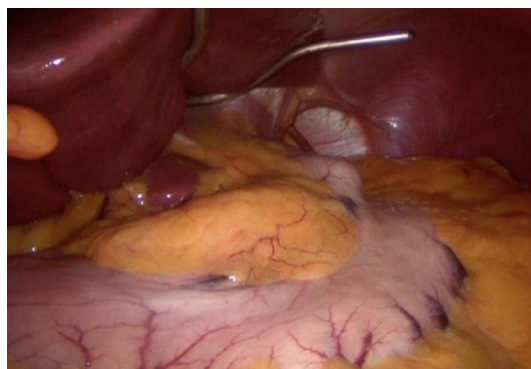


Figure 2. Retracted liver



Figure 3. Release and ligation of the omentum

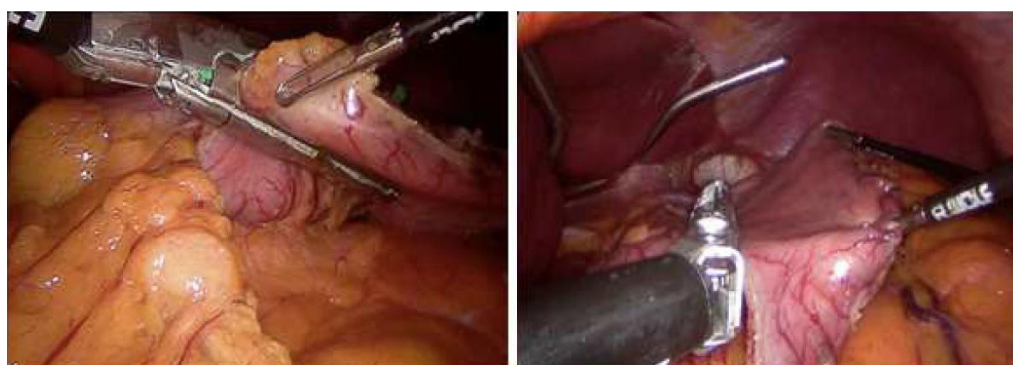


Figure 4. Insertion of first and second staplers from the 15-mm trocar

After the dissection of the greater curvature, a calibrating bougie (36F) is placed at the stomach and passed through the pylorus by the anesthesiologist. The first and second linear staplers are placed from the 15-mm trocar at the right upper quadrant to divide the stomach [Figure 4]. To avoid the narrowing at the incisura angularis, the first stapler is adjusted parallel to the pylorus. The first fired stapler and traction from the left trocar is very important to ensure a straight stapler line.

The remaining staplers are fired in cranially along the greater curvature of the stomach [Figure 5]. While black or green cartridges are applied to the first two firings, blue or purple cartridges are applied to the remaining part according to the thickness of the stomach. For transection, approximately 5-7 staplers are necessary to complete the transaction.

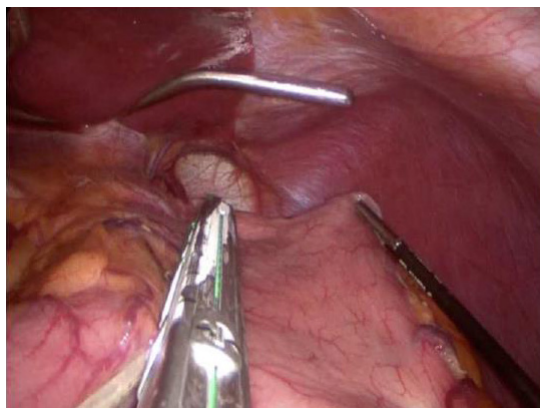


Figure 5. The stapler fired cranially

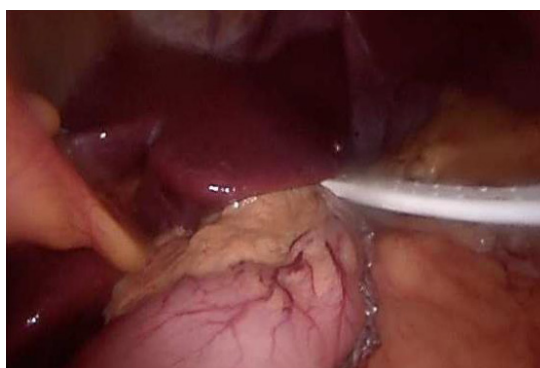


Figure 6. The gastric tube and the drain

During the transaction, clips are applied only to the staple joints and bleeding foci. Otherwise, no staple line reinforcement technique is used. If the twist is suspected, omentoplasty can be performed from three points as the antrum, incisura angularis, and its superior via suturing one by one. Methylene blue test is routinely applied to test for leakage. The resected stomach is removed from the left quadrant via a 12-mm trocar and a drain is placed from the right quadrant from a 15-mm trocar near the staple line [Figure 6]. All incisions are sutured after removing all trocars.

RESULTS

Patients are hospitalized approximately 2-4 days. On Postoperative Day 2, methylene blue test is done for leakage. According to the negative test, the regimen is started with water, tea, and soup. After adequate tolerance of oral fluids, the patient is discharged after the drainage catheter is removed. For the first two weeks, juicy foods are recommended; in the following two weeks, soft foods are recommended. According to tolerance, after the first month, solid food is started with the recommendation of less and frequent eating.

DISCUSSION

The number of sleeve gastrectomy procedures performed increases annually. This is clarified by the advantages of the simpler and faster technique; no malabsorption, anastomosis, or mesenteric surgery; no foreign body being inserted; and patients rarely having symptoms of “dumping syndrome”^[7]. In a consensus conference in 2014, LSG was accepted as a standalone procedure that reduces appetite and creates a

restriction. According to the consensus statement, LSG is a valid independent procedure and is a viable bariatric surgery option for high-risk patients, transplant candidates, and patients with lower BMI (30-35), patients with inflammatory bowel disease, and the elderly^[6].

Although LSG is currently the most commonly used technique in the bariatric surgical repertoire and is even considered as a gold standard technique, technical controversies continue. However, many discussion points on the procedure create a range probability without consensus: the distance from the pylorus, the routine use of intraoperative seal testing the size of the bougie used as a calibrator, the necessity for reinforcement of the staple line, and the considerations in case of revision LSG (re-LSG) requirement.

The end of the lower dissection is argumentative because the antrum is divided at 2 or 7 cm from the pylorus, determined by the surgical team^[8]. Sánchez-Santos *et al.*^[9], according to the results of the National Register of Spain, reported that they had better weight loss results in the follow-up of groups that started gastrectomy closest to the pylorus. Our reason for dissection 2-4 cm from the pylorus is to decrease the pressure in the gastric tube and allow preferable gastric emptying. It should be noted that the increase in pressure in the gastric tube is the main cause of leakages. Furthermore, gastric tube volume above and below incisura angularis and their ratio are important factors that affect weight loss. From our preliminary results published in 2018, an antrum volume of approximately one-third of the total remaining stomach volume appears to be ideal for optimal weight loss^[5]. Getting closer to the pylorus does not change weight loss and has a negative impact on using a non-touched antrum during revision surgery.

Another point of controversy is leak testing. The methylene blue test was initially defined to diagnose the post-gastrectomy fistulas. It is one of the most commonly used tests in bariatric surgery, consisting of oral administration of methylene blue and observation of any intraoperative outlet through the gastric tube^[10]. Methylene blue and/or air testing is recommended when the gastric tube is inserted into the distal esophagus and the antrum is clamped^[11]. There is a discrepancy between surgeons about which leak test they use, and whether it is performed^[12]. We apply methylene blue as a leakage test intraoperatively and on Postoperative Day 2. However, it should be kept in mind that a negative test does not warrant that there will be no postoperative complications including fistulas.

There is also the diameter of the remnant stomach in technical discussions about SG. Various evaluations have analyzed the results of surgery with different gastric tube calibration standards of more than 28-50 Fr. For example, Gagner^[13] defines an inverse relationship among the size of the bougie and the rate of leaks and support the use of catheters between 50 and 60 Fr. In the Fifth International Consensus Conference, it was recommended that a large bougie should be used (median was 36 French)^[14] and we also use 36 Fr.

Despite its simplicity, LSG can have serious complications. Gastric leakage is one of the most hesitated complications. Numerous maneuvers have been suggested to decrease the incidence of leak intraoperatively^[15]. Another discussion is in the reinforcement of the staple line. The main objectives of reinforcement of the staple line are to reduce hemorrhage rates and staple line leaks. There is no current consensus in recommendations about staple line reinforcement use. Its usage is surgeon-dependent and remains controversial^[16]. For instance, Bellanger *et al.*^[3] showed a series of 529 patients who did not leak without using any reinforcing material after the gastric section except fibrin administration. In a recent meta-analysis, there was no statistically significant difference in leak ratio. Therefore, we do not prefer reinforcement methods. According to our experience with more than 1000 patients, only three leakages, three bleedings, and one stenosis were detected as complications. Two of the three leakages were detected in the patient who underwent re-sleeve as revision surgery. While percutaneous drainage and the endoscopic stent were applied to one of these two leakages, the other was treated with re-laparoscopy drainage and stent. The third case of leakage was followed conservatively. In terms of hemorrhage, two

of the three bleeding cases were followed conservatively and they were discharged without any problem. Re-laparoscopy was performed when stabilization could not be achieved despite four units of blood replacement in only one bleeding case, but no bleeding focus could be detected and the bleeding had stopped. Only the hematoma was removed and the drain was replaced.

In up to 30% of cases, revision surgery is necessary for causes which include inadequate weight loss, weight re-gain, and/or the progress of severe upper gastrointestinal symptoms^[17]. Traditionally, conversion to DS after failed GS or more commonly to RYGB has been standard. The recently popular mini gastric bypass technique stands out in revision sleeve gastrectomies. It is important not only in revision of SG but also in revision of adjustable gastric banding^[18].

However, the discovery of a possible dilation of the remnant stomach or the presence of a remaining gastric fundus led to changes in the approach of a failed LSG and the application of a re-LSG emerged with the reason of re-sizing the sleeve when the expansion is present on the imaginary modalities^[19]. We do not recommend LSG as a revision surgery since two of our three leakage cases developed after re-sleeve operation. When re-sleeve is applied, we try to prevent narrowing by applying separate staplers between the antrum and the incisura angularis, without touching the incisura angularis, and on the dilated stomach.

CONCLUSION

We describe the tips and tricks for the sleeve gastrectomy technique. We also discuss the controversial subjects in this technique. Further prospective large studies would help to define optimal techniques. Standardizing this surgical technique as much as possible is important so most teams work using homologous methods, as well as in view of performing systematic reviews, consensus conferences, and long-term multicenter studies. We will see in time whether the fate of sleeve gastrectomy, which has been popular for the last 20 years, will follow that of the adjustable gastric band.

DECLARATIONS

Authors' contributions

Conception and design: Aktokmakyan TV

Administrative support: Sumer A

Provision of study materials or patients: Aktokmakyan TV, Gungor O, Sumer A

Collection and assembly of data: Aktokmakyan TV

Data analysis and interpretation: Gungor O

Manuscript writing: Aktokmakyan TV, Gungor O, Sumer A

Final approval of manuscript: Aktokmakyan TV, Gungor O, Sumer A

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Single-port laparoscopic myomectomy in the virgin womb - a retrospective analysis of 31 consecutive cases

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Abstract

Aim: We aimed to evaluate the feasibility of single-port laparoscopic myomectomy in the virgin womb.

Methods: A retrospective chart review of 31 consecutive cases between November 2017 and October 2019 performed by a single surgeon was performed.

Results: The mean age of patient was 50.10 ± 7.79 years old. The mean BMI was 23.55 ± 4.36 kg/m². The mean number of myoma in single patient was 3.84 ± 2.45 pieces. The mean maximum diameter of myoma in single patient was 11.24 ± 3.27 cm. The mean operation time was 182.32 ± 52.39 min. The mean blood loss was 231.77 ± 238.90 mL. The Visual Analogue Score (VAS) of pain when immediately arriving at the ward after operation was 2.32 ± 1.60 . The VAS after 24 h dropped to 1.23 ± 1.43 . In total, 119 myomas were removed in our study. There were 15 (48.4%) women with more than four myomas. Fifteen (48.4%) women had more than two myomas that were > 5 cm. There were 58 (48.74%) intramural myomas, with mean diameter of 6.72 ± 4.41 cm. Fifty-two (43.70%) subserous type myoma were removed with mean diameter 2.58 ± 3.35 cm. Posterior myoma accounted for five (4.20%) pieces with mean diameter of 9.30 ± 4.49 cm. The broad ligament type myoma accounted for four pieces (3.36%), and the mean diameter was 3.74 ± 1.87 cm. There were 51 (42.9%) myomas > 5 cm in diameter. Among the different types of myoma, there were 36 (62.1%) intramural type and 6 (11.5%) subserous type, and all posterior and broad ligament type were > 5 cm in diameter. The blood loss and operation time showed no relationship to



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myoma number. There were differences in blood loss ($P = 0.0359$) and operation time ($P = 0.0537$) based on the maximum diameter of myoma. No learning curve was noted in the cumulative sum control chart analysis of the 31 consecutive cases.

Conclusion: In our 31 consecutive cases, the operation time, blood loss, and postoperative VAS score were all comparable to the previously published literature for single-port laparoscopic myomectomy. It is feasible for virgin women with symptomatic myoma to receive single-port laparoscopic myomectomy.

Keywords: Single-port laparoscopy, myoma uteri, virgin

INTRODUCTION

Myoma uteri, a monoclonal smooth muscle cell tumor, is the most common benign gynecologic tumor in women in childbearing age. Its prevalence varies from 4.5% to 68.6% in different studies^[1] and tends to increase with age^[2]. The self-reported prevalence of myoma uteri is 1.8% in 20-29-year-old women, but it increases to 7.0% and 14.1% in the 30-39- and 40-49-year-old groups, respectively^[2].

The symptoms of myoma uteri are annoying and negatively impact the quality of life. Over one third of patients report heavy menstrual bleeding, prolonged duration of menstrual bleeding, and bleeding between periods^[2]. Moreover, over 50% of women with myoma uteri report having pain and abdominal cramps during periods, nearly one third report pressure on bladder or inside the abdomen, and nearly 25% feel pain during sexual intercourse^[2]. When asked about their symptoms in the last 12 months, over half (50.6%) of women with myoma uteri reported a negative impact on their daily life^[2]. Moreover, women with myoma uteri have significantly higher frequency of genitourinary symptoms including stress urinary incontinence, mixed urinary incontinence, urgency, daytime frequency, and dyspareunia^[3].

Women with myoma uteri can only receive observation when there are no symptoms. Symptomatic myoma needs either medical or surgical treatment. Medical treatment of myoma uteri includes levonorgestrel intrauterine system, tranexamic acid, non-steroid anti-inflammatory drugs, contraceptive pills, and oral or injected progestogens^[4]. These treatments can decrease menstrual blood flow or relieve pain, but are not effective in decreasing the size of the myoma. Gonadotropin releasing hormone analogs can effectively decrease myoma size and uterine volume^[5]. However, the side effects preclude its long-term use. Ulipristal acetate is a selective progesterone receptor modulator that exhibits direct tissue-specific partial progesterone antagonist effects. It is an effective option for both preoperative and intermittent treatment of moderate to severe, symptomatic uterine fibroids in women of reproductive age^[6]. However, the long-term effect is still not known, and in rare case it can cause severe liver damage^[4].

Surgery is a definite treatment for symptomatic myomas, especially for large ones. The bulky effect usually cannot regress quickly enough using non-surgical methods. Hysterectomy is performed if the patient does not want to preserve her uterus. Myomectomy is an alternative method if the patient chooses to preserve her uterus or the woman has not yet completed her childbearing. With the progression of minimally invasive surgery, many surgeons who are familiar with laparoscopic surgery will choose to perform laparoscopic myomectomy in those patients. Single-port laparoscopic myomectomy is more technically difficult but has comparable surgical outcomes^[7] to conventional laparoscopic myomectomy, with the benefit of good cosmetic results^[8]. In this study, we retrospectively analyzed the surgical outcomes of 31 women who had had no sexual experience with symptomatic myomas receiving single-port laparoscopic myomectomy without using uterine manipulator to preserve their virginity in our hospital performed by single surgeon.

METHODS

Study design

This was a retrospective chart review of consecutive 31 women without sexual experience who presented with symptomatic uterine myomas and received single-port laparoscopic myomectomy without using uterine manipulator between November 2017 and October 2019. The hospital setting is a regional teaching hospital (Kaohsiung Municipal Ta-Tung Hospital) but all staff are also members of a medical center (Kaohsiung Medical University Hospital) in Kaohsiung, Taiwan. All surgeries were done by the same gynecologist who is experienced in minimally invasive gynecologic surgery. The inclusion criteria were women with myoma uteri and symptoms such as menometrorrhagia, which causes anemia (Hemoglobin < 11 g/dL), or bulky effect, which cause bearing down sensation, frequency, tenesmus, back soreness, or a palpable pelvic/abdominal mass. The exclusion criteria were as follows: (1) malignancy could not be ruled out by image study; (2) patient was found to have severe adhesion or endometriosis requiring combined major operation at the same time; and (3) patient presented with complex medical condition before operation that required combined care by physician specialists. The largest diameter of myoma was recorded by image study (trans-abdominal ultrasound, abdominal CT, or pelvic MRI). The position and number of myoma was recorded during the operation. The operation time and blood loss were recorded by circulating nurse. The postoperative pain was recorded by charting nurse at bedside immediately when the patient arrived at the ward after operation and 24 h later. The pain score was measured by the Visual Analogue Scale. Postoperative fever over 38 °C and prolonged for 48 h was recorded as a complication. Other perioperative complications within 30 days were recorded. Patients were discharged from the hospital after well tolerating oral intake, successful ambulation, and absence of postoperative fever. All patients were scheduled for follow-up examinations at one week and one month after discharge.

Operation procedure

The patient is in the supine position. General anesthesia is selected and tracheal intubation is performed to maintain the airway. A single dose of cefazolin (1 g) is given by intravenous bolus method before operation. The dose is doubled if the patient's body weight is over 80 kg. A Foley catheter is inserted after anesthesia for bladder emptying. We do not use uterine manipulator in these women to preserve their virginity. A 1.5-cm vertical incision is done at umbilicus after sterile preparing and draping of abdomen and within 30 min of intravenous bolus antibiotics. A multi-instrument laparoscopic port (LagiPort™ Kit, Lagis, Taichung, Taiwan) is inserted through the umbilical incision and properly positioned. We insert a 10-mm telescope to view the pelvic cavity. The circulating nurse records the number and position of myomas. Before uterine incision is performed, diluted vasopressin (1:200 with normal saline) is injected around myomas until bleaching change is seen. We use cold knife scissors to cut the uterine surface until the body of the myoma is reached. An electrothermal bipolar tissue sealing system (LigaSure™, Medtronic Parkway, MN, USA) is used to control bleeding if necessary. After enough of the myoma body is revealed, a laparoscopic myoma screw is screwed into the myoma body for traction and direction. Then, further dissection of the myoma can be done step by step. After the myoma is removed from the uterine body, we use barbed suture to close the uterine wall defect for at least two layers in intramural type myoma. For superficial subserous myoma or broad ligament myoma, one-layered barbed suture is used if sufficient. After all uterine incisions are sutured, we apply fibrin sealant (Tisseel, Baxter AG, Vienna, Austria) on the suture surface to improve healing and decrease oozing. Large myomas are removed from the umbilical incision by cold knife morcellation. A multi-instrument laparoscopic port is placed again to check for bleeding under telescope. Then, 800 mL of 4% Icodextrin solution (Adept, Baxter AG, Vienna, Austria) are infused into the pelvic cavity after clearing blood clot to prevent adhesion. The umbilical incision is sutured layer by layer. All the apparatuses used in our surgery are conventional laparoscopic instruments; no articulated instruments were used in our study.

Table 1. The demographic data of patient in chronological series

	Age	BMI (kg/m ²)	Number of myoma	Max diameter of myoma (cm)	Operation time (min)	Blood loss (mL)	VAS score 1*	VAS score 2**
1	62	19.97	4	15	160	20	0	0
2	61	18.44	6	12	225	250	6	3
3	63	23.71	1	16	284	400	0	0
4	60	28.93	1	14	210	1000	0	3
5	59	19.94	3	14	195	150	4	2
6	58	32.18	3	9	165	400	1	0
7	57	26.00	8	14	290	300	0	2
8	56	19.96	3	9	160	100	3	2
9	54	27.04	4	12	220	410	4	6
10	55	22.77	1	10	105	10	2	2
11	53	18.44	7	7	145	100	0	0
12	52	21.66	2	16	280	450	2	0
13	51	26.58	1	8	195	50	3	0
14	50	18.75	7	10	222	20	3	0
15	49	37.19	2	12	208	150	2	0
16	48	24.49	4	8	135	180	0	0
17	48	23.28	5	8	135	150	3	0
18	46	19.98	3	8	130	50	2	2
19	41	24.68	10	10	231	50	0	2
20	48	21.15	1	10	190	200	2	3
21	49	26.02	4	20	205	900	2	0
22	46	21.72	6	8	130	55	4	2
23	47	24.50	2	12	142	300	3	0
24	51	25.31	6	10	173	250	3	2
25	42	25.05	1	15	240	100	5	0
26	32	17.48	1	15	75	100	4	0
27	45	17.50	2	13	117	10	2	1
28	34	25.89	7	8	190	500	3	2
29	38	20.39	6	6.5	150	250	3	2
30	44	26.64	3	9	155	20	3	0
31	54	24.54	5	10	190	260	3	2
Mean	50.10 ± 7.79	23.55 ± 4.36	3.84 ± 2.45	11.24 ± 3.27	182.32 ± 52.39	231.77 ± 238.90	2.32 ± 1.60	1.23 ± 1.43

*Patient arrived ward after operation; **24 h later after VAS score 1. VAS: visual analogue score

Statistical analysis

All data were calculated using JMP Pro 15 (SAS Institute Inc.) and Excel (Microsoft Inc.). The relationships of myoma number and size to operation time and blood loss were calculated by one-way ANOVA, with *P* value < 0.05 as significant. The control chart of learning curve was calculated by the cumulative sum control chart (CUSUM) method.

RESULTS

The demographic data of all 31 women are listed in Table 1. The mean age of the patient was 50.10 ± 7.79 years (95%CI: 47.24-52.95 years). The mean BMI was 23.55 ± 4.36 kg/m² (95%CI: 21.95-25.15 kg/m²). The mean number of myoma in single patient was 3.84 ± 2.45 (95%CI: 2.94-4.74). The mean maximum diameter of myoma in single patient was 11.24 ± 3.27 cm (95%CI: 10.04-12.44 cm). The mean operation time was 182.32 ± 52.39 min (95%CI: 163.11-201.54 min). The mean blood loss was 231.77 ± 238.90 mL (95%CI: 144.14-319.40 mL). The Visual Analogue Score (VAS) of pain when immediately arriving at the ward after operation was 2.32 ± 1.60 (95%CI: 1.74-2.91) and dropped to 1.23 ± 1.43 (95%CI: 0.70-1.75) after 24 h.

In Table 2, we describe the position and size of all myomas in all 31 patients in our study. Traditionally, posterior wall intramural myoma is thought to be more difficult to deal with laparoscopically, especially

Table 2. The position, number and size of myoma uteri of 31 patient (Original data)

Patient (myoma number)	Intramural	Subserous	Posterior intramural	Broad ligament
1 (4)	3 (6, 2, 1)*	1 (15)		
2 (6)	3 (12, 10, 8)	3 (1, 1, 1)		
3 (1)		1 (16)		
4 (1)				1 (14)
5 (3)	1 (14)	2 (2, 1)		
6 (3)	1 (9)	2 (3, 2)		
7 (8)	2 (14, 6)	6 (3, 2, 1, 1, 0.5, 0.3)		
8 (3)	1 (6)	2 (10, 1)		
9 (4)	2 (12, 8)	2 (3, 1)		
10 (1)	1 (10)			
11 (7)	3 (10, 6, 4)	4 (3, 2, 1, 0.5)		
12 (1)	1 (16)			
13 (1)				1 (8)
14 (7)	3 (8, 6, 5)	4 (10, 8, 1, 0.5)		
15 (2)	1 (12)	1 (3)		
16 (4)	1 (3)	2 (1, 1)	1 (8)	
17 (5)	3 (8, 7, 4)	2 (2, 0.5)		
18 (3)	2 (8, 6)	1 (1)		
19 (10)	10 (10, 4, 3, 2, 1.5, 1, 1, 1, 0.5, 0.3)			
20 (1)	1 (10)			
21 (4)	4 (20, 5, 4, 3)			
22 (6)	5 (8, 4, 3, 2, 1)	1 (0.5)		
23 (2)	1 (12)	1 (3)		
24 (6)	2 (10, 4)	4 (1, 1, 1, 1)		
25 (1)	1 (15)			
26 (1)			1 (15)	
27 (2)			2 (13, 5)	
28 (7)	2 (8, 7)	4 (4, 2, 1, 0.5)		1 (5)
29 (6)	1 (6.5)	4 (3, 2, 0.5, 0.5)	1 (5.5)	
30 (3)		2 (5, 3)		1 (9)
31 (5)	2 (10, 5)	3 (3, 2, 1)		
Total (average)	58 (6.72 ± 4.41 cm)	52 (2.58 ± 3.35 cm)	5 (9.30 ± 4.49 cm)	4 (3.74 ± 1.87 cm)

*number (size in centimeters)

when there is no uterine manipulator use. We divided them by the intramural type myoma and position. In total, 119 myomas were removed in our study. There were 58 (48.74%) intramural myomas, with mean diameter of 6.72 ± 4.41 cm (95%CI: 5.55-7.89 cm). Fifty-two (43.70%) subserous type myoma were removed with mean diameter 2.58 ± 3.35 cm (95%CI: 1.65-3.52 cm). Posterior myoma accounted for five (4.20%) pieces with mean diameter of 9.30 ± 4.49 cm (95%CI: 3.72-14.88 cm). The broad ligament type myoma accounted for four pieces (3.36%) and the mean diameter was 3.74 ± 1.87 cm (95%CI: 3.05-14.95 cm).

As shown in Table 3, the number of myomas > 5 cm in diameter was 51 (42.9%). There were 36 intramural myomas > 5 cm of 58 (62.1%), with mean diameter of 9.26 ± 3.46 cm (95%CI: 8.09-10.44 cm). The number of subserous type myomas > 5 cm in diameter was six of 52 (11.5%), with an average size of 10.67 ± 4.18 cm (95%CI: 6.28-15.05 cm). There were no changes in the posterior intramural type and broad ligament type myomas.

There were 20 (64.52%) women with more than three myomas in our study [Figure 1A]. When we deducted all the myoma < 5 cm, there were still 15 (48.39%) women with more than two myomas that were > 5 cm [Figure 1B]. The distribution of different types of myoma is shown in Figure 1C. Intramural myomas accounted for 48%, subserous myoma accounted for 44%, and posterior intramural myoma and broad ligament myoma accounted for 4% each. When only myomas ≥ 5 cm were included, intramural myoma

Table 3. The position, number and size of myoma uteri of 31 patient (Data of myoma size ≥ 5 cm)

Patient (myoma number)	Intramural	Subserous	Posterior intramural	Broad ligament
1 (2)	1 (6)	1 (15)		
2 (3)	3 (12, 10, 8)			
3 (1)		1 (16)		
4 (1)				1 (14)
5 (1)	1 (14)			
6 (1)	1 (9)			
7 (2)	2 (14, 6)			
8 (2)	1 (6)	1 (10)		
9 (2)	2 (12, 8)			
10 (1)	1 (10)			
11 (2)	2 (10, 6)			
12 (1)	1 (16)			
13 (1)				1 (8)
14 (5)	3 (8, 6, 5)	2 (10, 8)		
15 (1)	1 (12)			
16 (1)			1 (8)	
17 (2)	2 (8, 7)			
18 (2)	2 (8, 6)			
19 (1)	1 (10)			
20 (1)	1 (10)			
21 (2)	2 (20, 5)			
22 (1)	1 (8)			
23 (1)	1 (12)			
24 (1)	2 (10)			
25 (1)	1 (15)			
26 (1)			1 (15)	
27 (2)			2 (13, 5)	
28 (3)	2 (8, 7)			1 (5)
29 (2)	1 (6.5)		1 (5.5)	
30 (2)		1 (5)		1 (9)
31 (2)	2 (10, 5)			
Total (average)	36 (9.26 \pm 3.46 cm)	6 (10.67 \pm 4.18 cm)	5 (9.30 \pm 4.49 cm)	4 (3.74 \pm 1.87 cm)

accounted for 70%, subserous myoma dropped to 12%, posterior intramural myoma accounted for 10%, and broad ligament myoma accounted for 8% [Figure 1D].

As shown in Figure 2, we analyzed the relationship between the number of myomas and the blood loss, showing no significant relationship. We also calculated the relationship between the maximum diameter of myoma in a patient with the blood loss, showing a significant relationship.

We calculated the relationships between operation time and the number and maximum diameter of myomas. As shown in Figure 3A, there was no significant relationship between operation time and the number of myomas removed. The operation time became longer as the maximum diameter of myoma increased, but this relationship did not reach significance [Figure 3B].

As to the learning curve, we used the CUSUM method to calculate the learning curve by operation time [Figure 4]. No learning curve was noted in our study.

Concerning to perioperative complications, there were three cases (9.7%) with blood loss over 500 mL, but all could be corrected after intraoperative blood transfusion without any sequelae. There were three cases (9.7%) with postoperative fever $> 38^{\circ}\text{C}$ and persisted over 48 h. However, all subsided and the patients were discharged after three days of intravenous antibiotics. All 31 patients completed their surgery by single-port laparoscope without changing to multiport laparoscopy or laparotomy. There were no major complications such as bowel, ureter, bladder injuries, or incisional hernia.

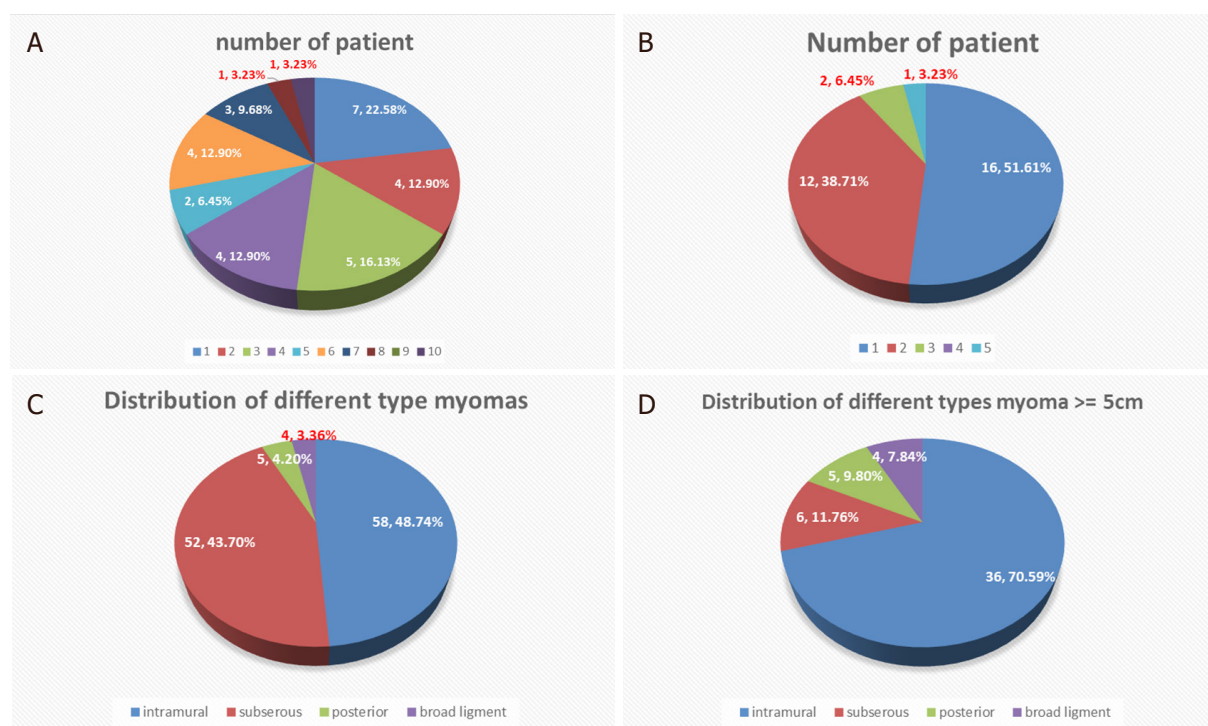


Figure 1. Distribution of relationship of patient and myoma. A: patient number and the myoma number; B: patient number with myoma ≥ 5 cm; C: distribution of myoma; D: distribution of myomas ≥ 5 cm

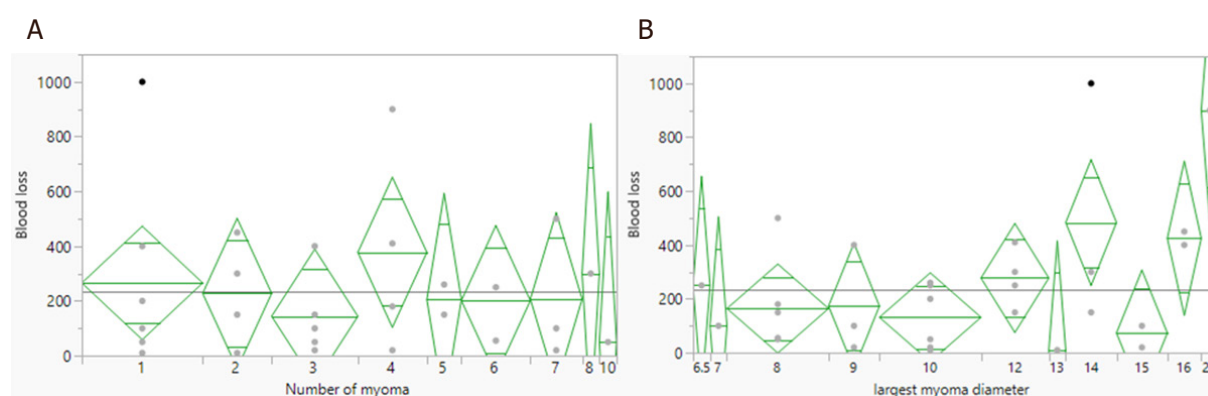


Figure 2. Relationship of blood loss and the number (A, $P = 0.9516$) and max diameter (B, $P = 0.0359$) of myoma

During the same period, we also had 10 cases of conventional laparoscopic myomectomy (using three trocars) and 10 cases of non-virgin single-port laparoscopic myomectomy (i.e., using uterine manipulator). We compare them in Table 4. The age was younger in those two groups (50.10 ± 7.79 vs. 42.6 ± 6.02 and 42.8 ± 4.69), and the maximum diameter of myoma was smaller in them (11.24 ± 3.27 cm vs. 7.30 ± 2.06 cm and 8.71 ± 2.05 cm). However, in BMI, number of myomas removed, operation time, blood loss, and VAS score when arriving at the ward and 24 h later, there were no significant differences among the three groups.

We compared our data to previous published literature concerning single-port laparoscopic myomectomy, and the results are shown in Table 5.

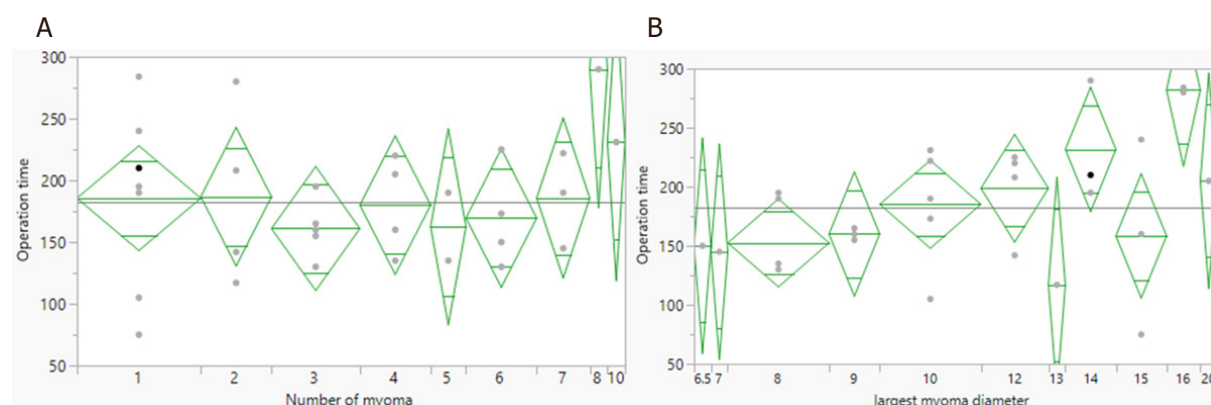


Figure 3. Relationship of operation time with the number (A, $P = 0.6378$) and max diameter of myoma (B, $P = 0.0537$)

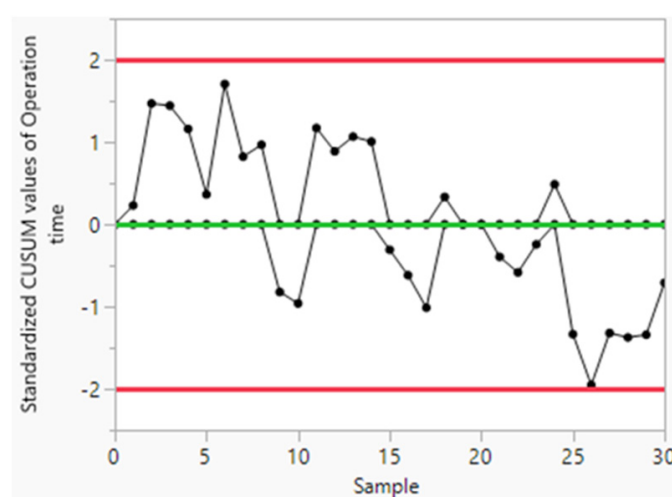


Figure 4. Control chart of operation time. CUSUM: cumulative sum control chart

Table 4. Comparison of single port laparoscopic myomectomy (virgin) group, single port laparoscopic myomectomy (nonvirgin) group and conventional laparoscopic myomectomy group

	Single port in virgin	Single port in non-virgin	Conventional 3 port	<i>P</i> value
Patient number	31	10	10	
Age	50.10 ± 7.79	42.6 ± 6.02	42.8 ± 4.69	0.0025*
BMI (kg/m ²)	23.55 ± 4.36	2.199 ± 2.90	24.45 ± 5.21	0.4337
Myoma number	3.84 ± 2.45	2.90 ± 1.73	2.60 ± 2.01	0.2413
Max diameter of myoma (cm)	11.24 ± 3.27	7.30 ± 2.06	8.71 ± 2.05	0.0008*
Operation time (min)	182.32 ± 52.39	152.10 ± 59.38	173.2 ± 76.36	0.3759
Blood loss (mL)	231.77 ± 238.90	102.50 ± 146.35	125.00 ± 206.07	0.1757
VAS score 1*	2.32 ± 1.60	1.00 ± 1.15	2.80 ± 2.53	0.0586
VAS score 2**	1.23 ± 1.43	0.20 ± 0.63	0.80 ± 1.03	0.0818

*Immediately arrived ward after operation; **24 hours later after VAS score 1. VAS: visual analogue score

DISCUSSION

Since the introduction of laparoscopic myomectomy in 1979 by Semm^[9], numerous studies have been published concerning the feasibility and safety of this minimally invasive method^[10-12]. When compared to open laparotomy myomectomy, laparoscopic myomectomy remains a safe and effective surgical option with the advantages of a lower drop in hemoglobin^[13], less postoperative pain, and faster recovery^[14].

Table 5. Comparison of surgical outcomes with previous published studies^[18,19,21-24]

	Our studies	Previous published studies
Mean number of myoma	3.84 ± 2.45	1-3 to 1-5
Mean diameter of max myoma (cm)	11.24 ± 3.27	7-14
Operation time (min)	182.32 ± 52.39	77.5 ± 37.8 to 191.4 ± 103.0
Blood loss (mL)	231.77 ± 238.90	114.2 ± 157.0 to 224.6 ± 320.9
VAS score	2.32 ± 1.06*	1.60 ± 1.30 to 3.50 ± 0.8
	1.23 ± 1.43**	

*Immediately arrive ward after operation; **24 hours later. VAS: visual analogue score

Concerning the obstetric outcome, both groups show no significant differences in pregnancy rate, abortion rate, and preterm delivery rate^[14].

Recently, technological innovations (such as a multichannel single port, articulating instruments, and high-definition laparoscopes) have allowed laparoscopic surgeons to perform gynecologic surgery through only one small incision over the abdomen (single-port laparoscopic surgery) with the aim of further reducing the invasiveness of conventional laparoscopy. There are many reports applying this new method to gynecologic surgeries such as hysterectomy, adnexal surgery, or even cancer surgery^[15-17]. Its use in myomectomy is limited to advanced laparoscopic surgeons due to the difficulty of multiple suturing and tying^[7]. However, there are more and more reports on the feasibility and safety of this difficult method^[18-22].

In a systematic review and meta-analysis comparing single-port laparoscopic myomectomy with conventional laparoscopic myomectomy published in 2019, Kim *et al.*^[19] concluded that single-port laparoscopic myomectomy is comparable to conventional laparoscopic myomectomy in terms of safety and feasibility and more advantageous in terms of immediate postoperative pain. However, virginity is not mentioned in the literature they included. To the best of our knowledge, this is the first study reporting on the use of single-port laparoscopic myomectomy in virgins.

As is known, it is more difficult in laparoscopic gynecologic surgery to not use a uterine manipulator, especially in myomectomy, which needs the uterine manipulator to change the position of the uterus for proper surgical plane when dissecting myoma and suturing the uterine wall defect.

In our study, the mean number of myoma in a single patient was 3.84 ± 2.45, which is comparable to previous studies^[18,19,21-25], which range from 1-5. However, in one patient in our study, 10 myomas were removed in the same operation, which we believe is the most reported in the literature in a single-port laparoscopic myomectomy. The mean diameter of maximum myoma in single patient was 7-14 cm in those studies, and in our study was 11.24 ± 3.27 cm. The maximum diameter of single myoma removed in our study was 20 cm, which we believe is the largest diameter of myoma removed by single-port laparoscopic surgery reported in the literature. The mean operation time in our study was 182.32 ± 52.39 min, which is also comparable to those studies (from 77.5 ± 37.8 min to 191.4 ± 103.0 min). The mean blood loss was 231.77 ± 238.90 mL in our study. The mean blood loss in previous studies ranges from 114.2 ± 157.0 mL to 224.6 ± 320.9 mL. However, there were two extreme values in our study, while the median value of blood loss was 150 mL. We believe the blood loss is comparable to those previous studies. The VAS score in our study was 2.32 ± 1.06 when patients arrived at the ward after operation and 1.23 ± 1.43 24 h later, which is also comparable to those studies (from 1.60 ± 1.30 to 3.50 ± 0.8).

In total, 119 myoma were removed in our study, with 51 (42.86%) being > 5 cm in diameter. All the posterior intramural and broad ligament type myomas were > 5 cm. Overall, 36 of 58 (62.1%) intramural myomas were > 5 cm. Most subserous type myomas were small; only 15 of 52 (28.8%) were > 5 cm. These results are similar to the reference values.

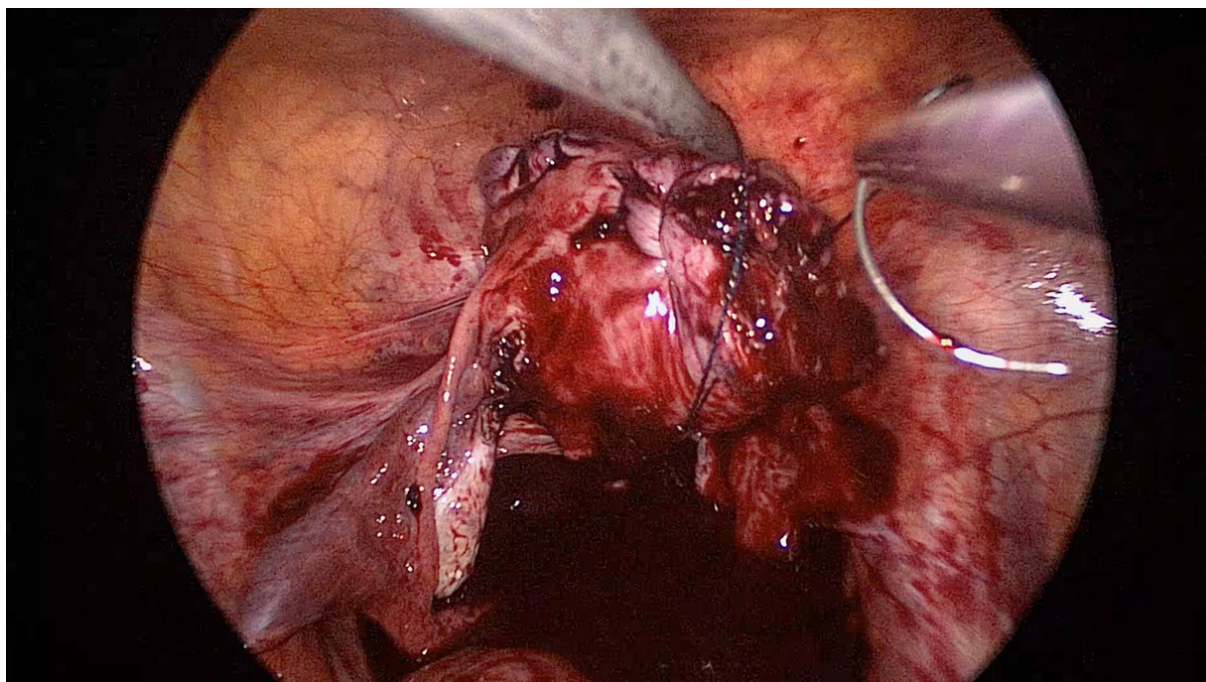


Figure 5. Traction of uterus by holding suture string near uterine wall defect

Traditionally, it is thought that intramural type myoma, especially positioned in posterior uterine wall, is more difficult to remove laparoscopically. It needs elevation of the uterus by uterine manipulator to reveal the myoma. Besides, it is difficult to suture the posterior uterine wall defect in a relatively small space (posterior cul-de-sac). In our study, we did not use uterine manipulator to preserve the patient's virginity. We elevated the uterus by one apparatus and used barbed suture. Then, we could manipulate the uterus by holding the string near the uterine defect [Figure 5]. The benefit of this method is that we could correctly suture on the right plane and angle one at a time.

The relationship of blood loss to the number of myoma removed was insignificant. It might be due to the subserous myoma accounting for a substantial portion of the multiple-myoma patients. However, we did not find any description of the relationship between myoma number and blood loss in the literature. The blood loss was higher when the maximum diameter of myoma was larger. This is reasonable because the greater is the size of the myoma, the narrower is the space in the operation field, which may make it difficult to control bleeding by apparatus when it occurs.

There was no significant relationship between operation time and the myoma number removed. We think it is for the same reason: a substantial portion of multiple myomas was subserous type, which could be removed without difficulty. The operation time was longer when the maximum diameter of myoma became greater, but did not reach significance. We think it is reasonable that removing large myoma is time consuming whether during excision, suturing defect, or removing from the umbilical incision by cold knife blade.

There was no learning curve according to the CUSUM analysis in our study. It may be because the operator is experienced and already familiar with single-port laparoscopic surgery. For those not familiar with single-port laparoscopic surgery, a learning curve may exist to overcome the technical difficulty^[26]. However, Torng *et al.*^[27] concluded that a learning curve is not required for laparoendoscopic single site surgery for experienced laparoscopic surgeons.

There is scant literature on the topic of laparoscopic gynecology surgery in virgins. Most of the reports are for diagnostic purposes^[28] or case studies on adnexal surgery^[29-35]. There is one case report on performing a posterior colpotomy laparoscopically to remove a prolapsed myoma in a virgin's vagina^[35] to preserve her virginity. However, this is done by multiport laparoscope. There is a retrospective study of 297 cases of laparoscopic-assisted vaginal hysterectomy in virgins and nulliparas using Biswas uterine vaginal elevator^[36], but the elevator should be removed laparoscopically after uterus is excised completely. It is not suitable in laparoscopic myomectomy because colpotomy is not necessary. Furthermore, this research is done by multiport laparoscopy.

For virgins with symptomatic myoma, medical treatment can be used. Ulipristal acetate can achieve amenorrhea state sooner than placebo^[37] and improves quality of life^[38]. In some research, it is used preoperatively, but the benefit is inconclusive^[39]. However, there are sporadic cases of liver injuries and hepatic failure reported, and its use should be restricted to those whose liver condition is healthy, and periodic liver monitoring before, during, and after treatment is suggested^[40]. The long-term effect of ulipristal acetate on pregnancy still lacks high quality data. Besides, for patient with large myoma, the mass effect does not disappear with its use. Thus, surgery is needed in these patients.

Uterine artery embolization (UAE) is another choice for those group. According to the 10-year outcomes of the randomized EMMY (Embolization *vs.* Hysterectomy) trial, about two thirds of hysterectomies can be avoided and health-related quality of life remains comparatively stable. However, 35% of patients need secondary hysterectomy after UAE^[41]. Furthermore, the pregnancy rate was found to be lower and miscarriage rate higher after UAE than after myomectomy^[42].

High intensity focused ultrasound is a newer method for treating myoma. The response rate ranges 40%-85% in different modalities and studies^[43]. However, it is expensive in Taiwan, and the mass shrinks slowly. The long-term effect of high intensity focused ultrasound treatment is still not clearly known for myoma.

Surgery is the only way to remove mass and improve symptoms, especially mass-induced ones. The specimen can be obtained by pathologic examination.

The limitation of this study is that it was a retrospective chart review. Further large-scale randomized research is needed to compare with other methods to clarify its limitations and safety.

In conclusion, this is the first report on single-port laparoscopic myomectomy on the virgin womb. In our 31 consecutive cases, the operation time, blood loss, and postoperative VAS score were all comparable to the previous published literature. Without using uterine manipulator, we could still complete the operation successfully without major complications. The manipulation of the uterus could be achieved by myoma screw or suture string when needed. It is feasible for virgin women with symptomatic myoma to receive single-port laparoscopic myomectomy.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Technical Note

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Uniportal video assisted thoracoscopic left upper bronchial sleeve lobectomy in a pediatric patient

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Abstract

Endo-bronchial tumors are sporadic in the pediatric population. Pneumonectomy is rarely indicated and best to be avoided if possible due to the morbidity it may cause. In children, preserving as much of the lung parenchymal tissue as possible is crucial and maintaining the integrity of the "still maturing" chest wall may reduce the risk of developing scoliosis and chest deformities in the future. The integration of minimally invasive surgical techniques and parenchymal sparing procedures represents the best possible outcome for these patients. Of course, oncological principles should be re-spected when such a procedure is performed. We present the first report in the literature of a "left" upper lobe sleeve resection in an 8 year old patient via a single port video-assisted thoracoscopic surgery technique.

Keywords: Uniportal video-assisted thoracoscopic surgery in pediatrics, minimally invasive thoracic surgery in children, video-assisted thoracoscopic surgery sleeve lobectomy in pediatrics, pediatric thoracic surgery, bronchial carcinoid tumour in pediatrics, uniportal video-assisted thoracoscopic surgery sleeve lobectomy

INTRODUCTION

Thoracic surgery has recently undergone significant transformation and evolution. The traditional (open) thoracotomy has started to lose its popularity and thoracoscopic surgeries have started to gain interest amongst most surgeons. This is largely because of the benefits in reducing the proportion of postoperative



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Figure 1. Bronchoscopic image showing a pedunculated mass occluding the left main stem bronchus

complications and an earlier return to normal life. Uniportal video-assisted thoracoscopic surgery (VATS) is the latest development in thoracoscopic surgery^[1]. After a decade of developing and adapting thoracoscopic surgery to a variety of thoracic conditions, it has now become possible to perform the most complex procedures through this technique, especially in adults^[2-4]. However, this is still rarely utilized in children due to the difficulty of instrumentation and the lack of experience. Neuroendocrine tumours compose a small percentage of lung tumors not exceeding 2% of the general population. Neuroendocrine tumors however, are considered the most common airway malignancy in children^[5]. It is well-known and generally accepted that surgical resection is the ideal solution in these cases^[5]. The rarity of these tumors usually results in a significant delay in their diagnosis and treatment, as it may be treated for a long time as a chronic infection or foreign bodies in the respiratory tract^[6]. Since the first bronchial sleeve operation was performed in the 1940s^[7], these operations have evolved to become the preferred procedure to avoid pneumonectomies^[8], and have recently been performed via the uniportal VATS technique with excellent results^[3,4]. Except in one case by Gonzalez-Rivas *et al.*^[9], these operations have not been performed previously with the uniportal VATS technique. In his article, Gonzalez-Rivas *et al.*^[9] performed a right upper sleeve lobectomy and tracheoplasty in a 10-year-old child for a carcinoid tumor in the right main bronchus. In the current study, we report the second successful case of bronchial sleeve resection in a child through the uniportal VATS technique in the literature, and the first to be performed on the left main bronchus in an 8-year-old child with satisfactory results.

CASE PRESENTATION

A previously healthy 8-year-old female patient with a six-month history of fever and recurrent chest infections showed only partial improvement with antibiotics. A bronchoscopy was performed to rule out the presence of a foreign body, and to obtain samples for microbiology. A highly vascularised endobronchial mass arising from the left main bronchus and occluding the bronchus to the upper lobe was found [Figure 1]. Transbronchial biopsy and bronchoalveolar lavage were performed. Pathological findings revealed a typical carcinoid tumor and cultures grew *Pseudomonas aeruginosa*. i.v. antibiotics were given according to culture sensitivities and a 68Ga DOTATATE PET-CT was performed to exclude mediastinal and extrathoracic findings [Figure 2]. The case was discussed at the multidisciplinary team meeting and surgery was recommended. To avoid pneumonectomy at this young age, a bronchial sleeve resection was considered. Based on our experience in uniportal VATS operations in adults at a specialized and ultra-high volume tertiary center^[10], and after gaining further experience in paediatric patients^[11], we decided

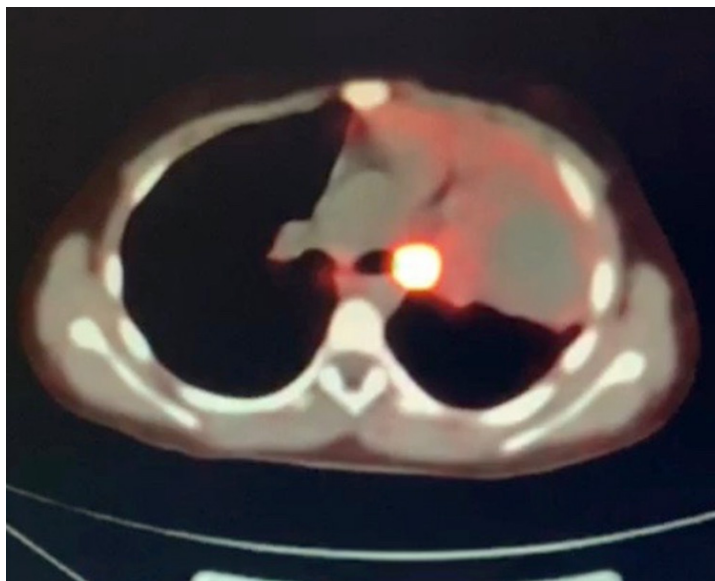


Figure 2. 68Ga DOTATATE PET-CT shows high uptake in a left main bronchus mass



Figure 3. Right decubitus positioning of the patient

to perform the surgery via the uniportal VATS technique to reduce the risk of complications and surgical trauma.

Surgical technique

Once under general anesthesia, isolated right lung ventilation was maintained with a 26 Fr “right” double lumen endotracheal tube. The patient was positioned in the right decubitus position [Figure 3]. The uniportal VATS approach required a 3-cm incision at the 5th intercostal space, along the anterior axillary line. A high definition thoracoscope with 30°/10 mm lens was inserted through the incision. Exploration of the pleural cavity revealed severe adhesions, probably due to recurrent chest infections. After adhesiolysis,

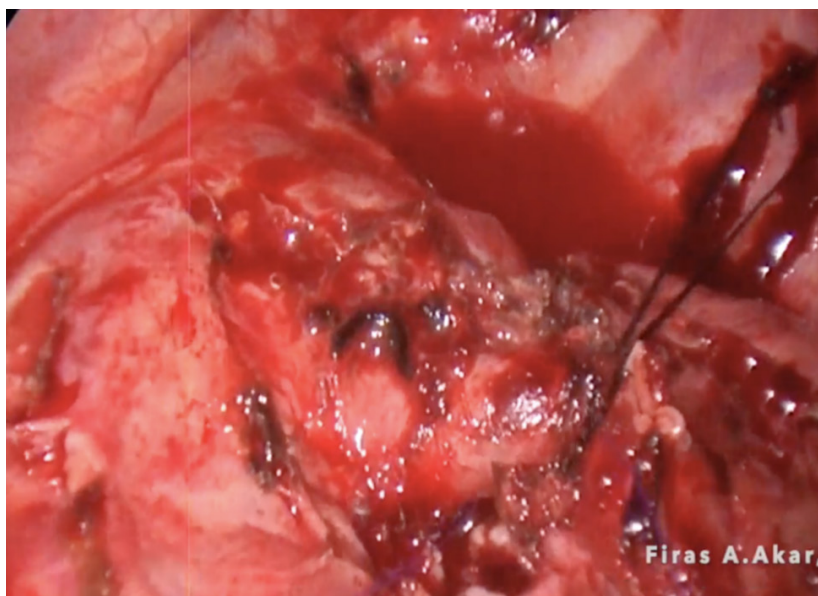


Figure 4. Intraoperative image showing the way of retracting the left main pulmonary artery to improve exposure of the bronchus

a left upper bronchial sleeve lobectomy was performed. First, the left superior pulmonary vein was dissected free, encircled and then divided using Endo-GIA Stapler vascular reload (Endo GIATM Curved Tip Reload with Tri-StapleTM Technology). After that, branches of the pulmonary artery to the upper lobe were divided individually after tying with 0 silk thread or double clipped with polymer clips Click'aV PlusTM until the artery was completely separated from the upper lobe [Video 1]. The left main and left lower lobe bronchus were freed circumferentially by scalpel and surgical scissors before the lobe was retrieved inside a protecting bag. Frozen section confirmed disease-free margins. The inferior pulmonary ligament was divided, and the left main pulmonary artery was retracted laterally using 0 silk stitch encircled around the artery and fixed to the chest wall [Figure 4], to both avoid tension and facilitate the subsequent anastomosis respectively. The left lower lobe and left main bronchus were anastomosed end to end using a continuous PDS 4/0 double needled suture, starting from the medial aspect of the bronchus and ending by tying the suture at the lateral corner of the anastomosis [Video 1]. Upon completion of the anastomosis, an air-leak test was done and inflation of the lower lobe was ensured. After adequate hemostasis, a single 20 Fr chest tube was inserted through the same incision and the wound was closed in layers in standard fashion. The patient was successfully extubated and transferred stable to the pediatric ICU. The post-operative course was uneventful otherwise and the patient was stepped down to the ward 24 h post-surgery. Postoperative chest X-ray showed good expansion of the left lower lobe [Figure 5]. The chest tube was removed on post-operative day 5, and the patient was discharged home on post-operative day 6 in an excellent condition. Follow-up bronchoscopy (at 1 and 6 months after the procedure) revealed intact anastomoses with no evidence of stenosis. At 9 months' follow-up, the patient is asymptomatic and does not have any complaints.

DISCUSSION

Sleeve bronchial resection procedures are usually performed in adults to avoid pneumonectomy and associated morbidity. These operations are conducted in cases of central or endo-bronchial tumours. In children, bronchial sleeve resections are extremely uncommon and rarely indicated due to the paucity of lung malignancies in the pediatric population in general, especially endobronchial tumors. A review of the literature only yielded one case of a bronchial sleeve operation performed via the uniportal VATS technique in a 10-year-old child who had a carcinoid tumour in the right main bronchus^[9]; there were otherwise only a few reports on pediatric sleeve resection through the traditional open thoracotomy approach^[9,12]. It is well

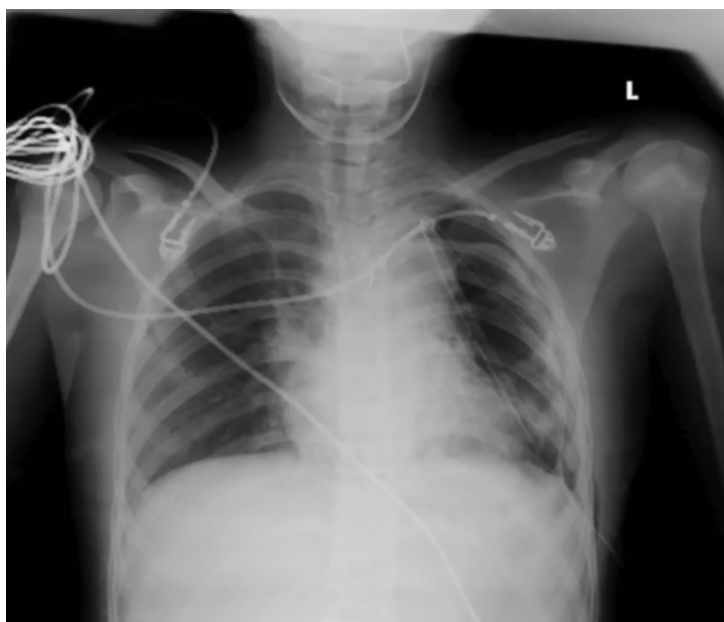


Figure 5. Postoperative chest X-Ray showing good inflation of the lung with no abnormalities

known that VATS can significantly reduce complications and surgical trauma, contribute to earlier recovery and expedite the return to normal life for patients^[13].

There are additional benefits of thoracoscopic surgery, especially in children, such as the avoidance of scoliosis and preventing breast asymmetry in females due to the damage that may occur in chest wall muscles from traditional open thoracotomy^[14-16]. Therefore, the thoracoscopic approach to these pediatric cases is much more desirable and should be strongly encouraged. There are still some obstacles that may limit the applicability of this technique in children however, with the learning curve being particularly steep. The operative field available in the child's pleural space is limited, which can lead to extreme challenges with instrumentation. Another difficulty that one may face during surgery is the complexity of lung isolation due to the unavailability of the double-lumen tube for all ages, which poses a challenge to the surgeon and anesthesiologist. This is on top of the lack of instruments specially designed for pediatrics. We usually use traditional instruments to perform uniportal VATS in infants^[11], or those designed for adults in older children.

In conclusion, we strongly believe in the value and benefits of uniportal VATS surgery, especially in pediatric patients. Complex operations via the uniportal VATS approach as described is feasible in children. However, experience in uniportal VATS is necessary, and these operations must be performed in specialized and high-volume centers that contain all the necessary facilities. There is a need to develop specialized equipment specific for children for such operations to make it more manageable.

DECLARATIONS

Authors' contributions

Conception and design of the study, and performed data analysis and interpretation: Abu Akar F, Shaqqura B

Performed data acquisition, as well as provided administrative, technical, and material support: Abu Akar F, Rumman N, Soultanis KM

Availability of date and materials

The authors declared that all data that support our findings can be found in our database and archive at Al-Makassed Hospital. Data can be deposited into data repositories or published as supplementary information in the journal.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval and consent was obtained from the patient's parents to publish the article.

Consent for publication

Not applicable.

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Technical Note

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Endoscopic-assisted ICG (EASI) technique for sentinel lymph node biopsy in breast cancer

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Abstract

Sentinel lymph node biopsy is currently the standard of care for axillary staging in early breast cancer patients with no clinical or radiological evidence of axillary lymph node involvement. Novel techniques studied in recent years include the use of indocyanine green (ICG) fluorescence imaging, which was reported in a recent network meta-analysis to be comparable to standard dual modality in terms of false negative as well as detection rate. However, there have been no standardized operative methods leading to the underutilization of this modality in clinical practice. In addition, technical limitations such as the difficulty in tracing ICG flow in obese patients further restrict the use of ICG fluorescence in sentinel lymph node biopsy. In this article, we describe in detail the use of the endoscopic-assisted ICG technique in performing sentinel lymph node biopsy, which addresses limitations associated with conventional use of ICG fluorescence imaging. The technical novelty of this technique lies in the fact that it has not been previously described in the literature and it allows for the identification of sentinel lymph nodes with minimal incision and tissue disruption as well.

Keywords: Endoscope, endoscopic, endoscopic-assisted, EASI, indocyanine green, fluorescence, novel technique, minimally invasive, minimal access

INTRODUCTION

The most widely used technique for sentinel lymph node (SLN) identification is the dual-modality method involving the injection of technetium-99m-labeled nanocolloid and blue dye into the peritumoral or



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Figure 1. Injection of indocyanine green in the periareolar region



Figure 2. Visualization of indocyanine green under fluorescence imaging

periareolar region^[1]. The dual technique has its shortcomings, including radiation exposure to healthcare professionals and patients, issues with radiotracer availability, dependency on availability of nuclear medicine units and allergic reactions to blue dye. New techniques have been developed to improve the clinical value of SLN biopsy with similar accuracy, but avoiding irradiation and risks of allergy^[2]. Novel techniques studied in recent years include those using indocyanine green (ICG) fluorescence imaging, which was reported in a 2019 network meta-analysis by Mok *et al.*^[3], showed ICG to be superior to the blue dye technique alone and comparable to that of the standard dual-modality method. There was, however, technical difficulties with the use of ICG^[4] especially in obese patients, thereby limiting the widespread use of this modality. In this article, we describe a minimally invasive technique which is effective in overcoming limitations and at the same time minimizes tissue dissection or disruption in the axilla.

TECHNIQUE

Detailed description of this technique as attached in [Video 1](#).

ICG PREPARATION AND INJECTION

ICG VERDYE (Diagnostic Green, Bavaria) solution of 1.25 mg/0.5 mL (vial of 25 mg added to 10 mL of water for injection) was prepared, and 1 mL of ICG was injected intradermally over 12 o'clock and 9 or 3 o'clock (right and left breast, respectively) with 0.5 mL per injection site after induction of general anesthesia [Figures 1 and 2]. Special care was taken to avoid contamination of surgical field with ICG to reduce artifacts under fluorescence imaging [Figure 3]. A 5-min waiting time was advised to allow for adequate lymphatic flow to the axilla. Lymphatic flow could be visualized under fluorescence imaging [Figures 4 and 5]

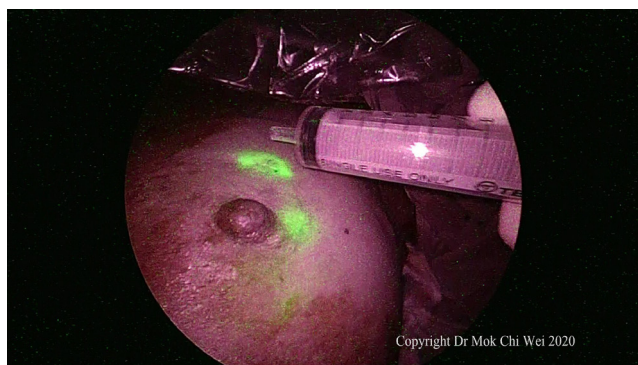


Figure 3. Gentle tap at the injection site to stimulate lymphatic flow. An empty syringe was used to avoid contamination of the surgical field

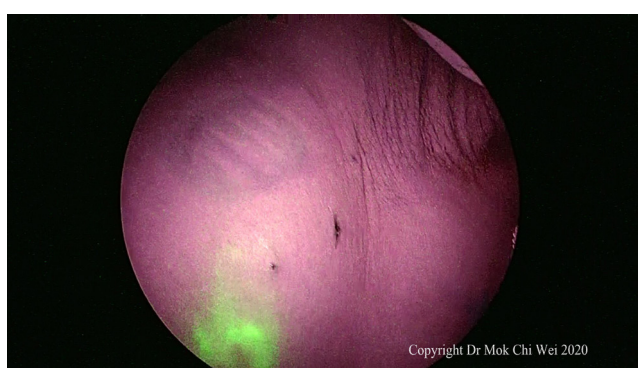


Figure 4. Lymphatic flow can be visualized and lymph fluid observed flowing towards the axilla, via overlay mode

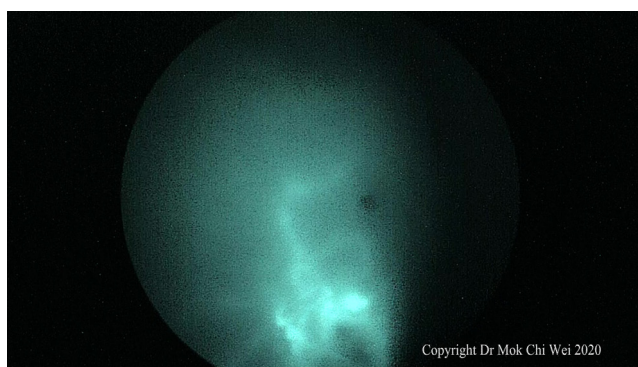


Figure 5. Lymphatic flow can be visualized and lymph fluid observed flowing towards the axilla, via pure fluorescence mode

to aid in determining the most optimal placement of the axillary incision. Alternatively, a direct axilla incision could be made within the axillary skin crease without prior identification of lymphatic flow.

ENDOSCOPIC-ASSISTED ICG TECHNIQUE AND IDENTIFICATION OF SENTINEL LYMPH NODES

The endoscopic-assisted ICG (EASI) technique involved the use of an optical trocar (Endopath Xcel® Bladeless Trocar, Johnson & Johnson, USA), a 5- or 10-mm 0° or 30° endoscope and ICG system (Olympus Visera Elite II, Olympus, Tokyo, Japan) in performing the SLN biopsy. A 5- or 10-mm stab incision

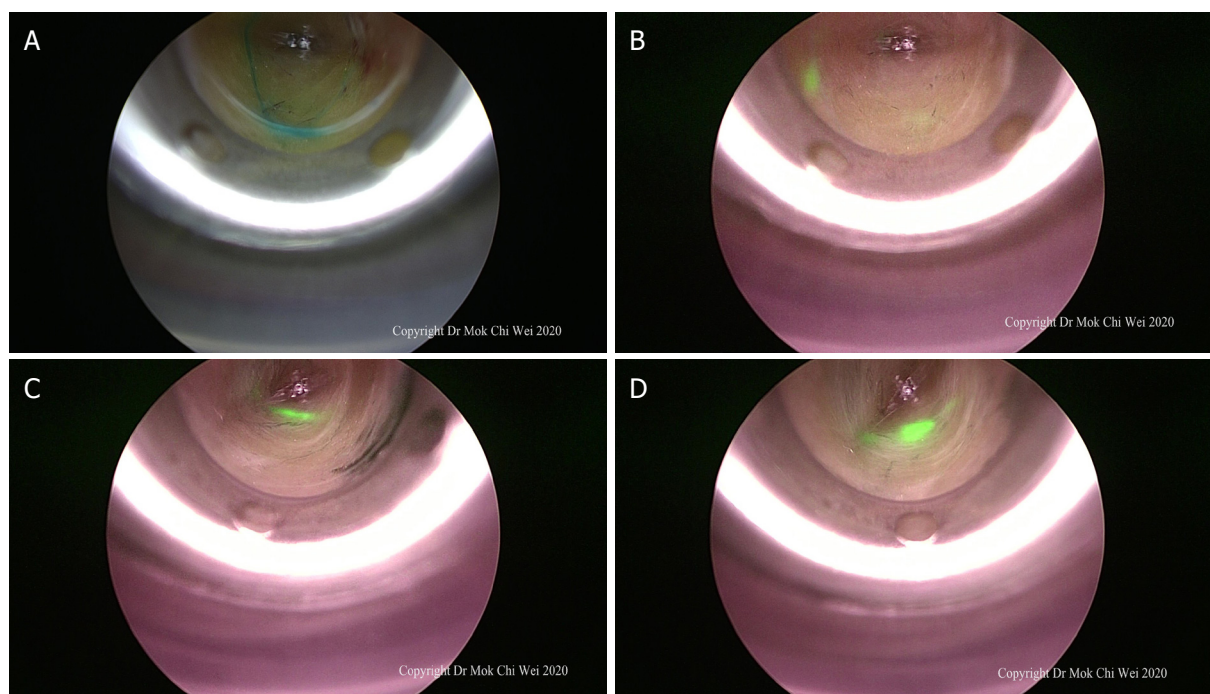


Figure 6. A-D: after a stab incision was made, direct optical entry using a bladeless trocar was performed and lymphatic flow was observed (either blue dye or indocyanine green) until the first sentinel lymph node was visualized under endoscopic guidance

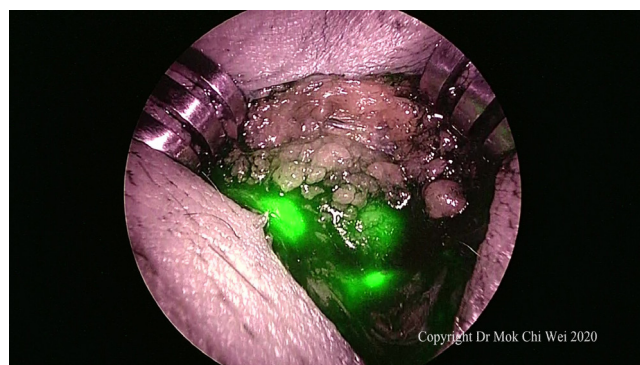


Figure 7. After identification of the first sentinel lymph node, the stab incision was extended to allow for a focused dissection as well as retrieval of the first sentinel lymph node. Subsequent sentinel lymph node were retrieved as well if any and sent for intraoperative frozen section analysis

(depending on the endoscope used) was placed along the axillary skin crease. In our institution, blue dye was used concomitantly with ICG as a second modality. Direct optical entry was performed with slow and controlled movement while looking for lymphatic flow, either blue or green (under fluorescence imaging) [Figure 6]. Direction of entry was then guided by lymphatic flow until the first SLN was identified.

RETRIEVAL OF SENTINEL LYMPH NODES

Once the first SLN was identified, the camera was then removed. With the optical trocar still in place, minimal extension of the skin incision to 1.5 or 2 cm was then performed to allow retrieval of the SLN. A focused and directed dissection towards the SLN as guided by the optical trocar resulted in minimal tissue/lymphatic disruption or damage [Figures 7 and 8]. After retrieval of the first SLN, fluorescence imaging was then used to trace the lymphatic flow beyond the first SLN and detect further SLNs, if any [Figures 9 and 10].



Figure 8. Sentinel lymph node retrieved showing indocyanine green under fluorescence imaging

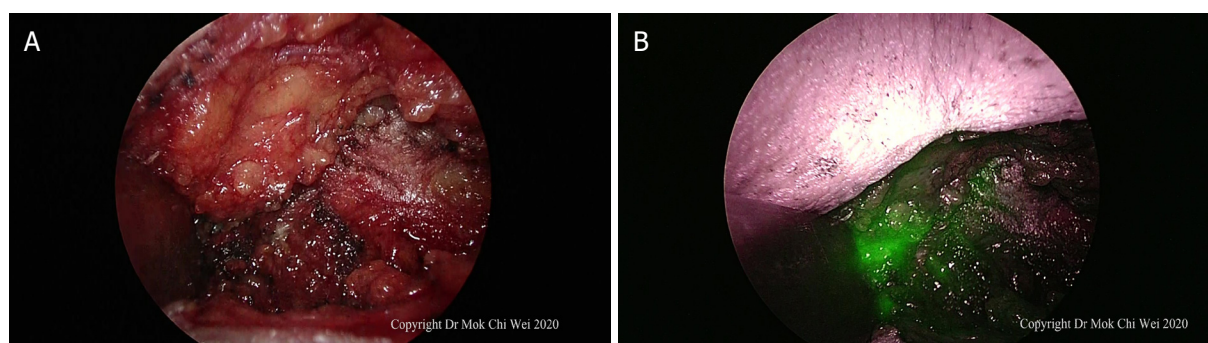


Figure 9. A, B: axilla examined under direct vision/palpation as well as indocyanine green fluorescence imaging. In [Figure 9B](#), as the axilla showed an area of indocyanine green fluorescence without any clinically palpable nodes, the area was excised to ensure that it was just lymphatic flow (false positive) rather than sentinel nodes

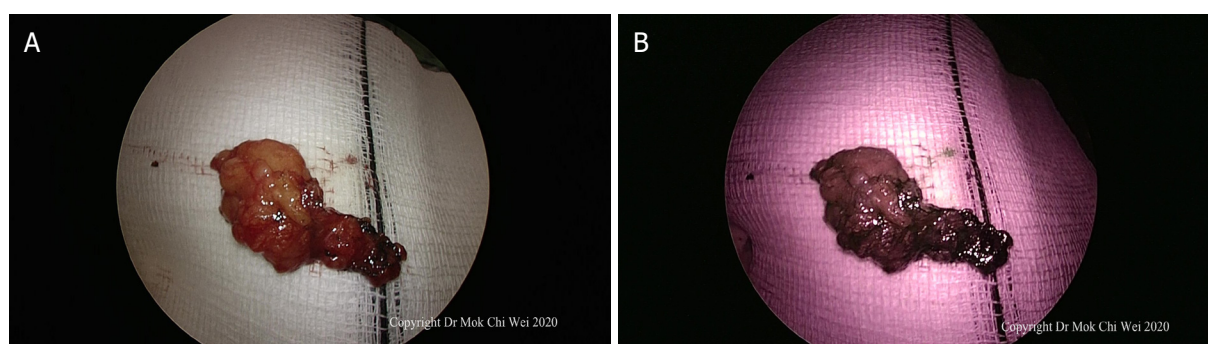


Figure 10. A, B: after excision, the tissue was examined under white light as well as fluorescence mode, confirming that there were no further sentinel lymph nodes and that the area of fluorescence shown in [Figure 9B](#) was indeed a false positive observation

In cases where dual modality was used, the second technique could be used to detect SLNs that were not ICG-avid. Nodes were sent for intraoperative frozen section analysis and axillary dissection performed as deemed necessary if the frozen section analysis returned positive for metastatic carcinoma.

CONCLUSION

The EASI technique for SLN biopsy is an innovative approach to utilize ICG in SLN biopsy with the potential to overcome the difficulty of visualizing ICG flow especially in obese patients as well as resulting in minimal tissue/lymphatic disruption.

DECLARATIONS

Authors' contributions

Conception and design of the study: Mok CW, Hing JXJ, Shetty SS

Drafting of manuscript: Mok CW

Revision and preparation of final manuscript: Mok CW, Hing JXJ, Shetty SS, Tan SM

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained as appropriate.

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Perspective

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From TATA to single port robotic (SPr) taTME: approaches to distal rectal cancer

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Abstract

The surgical management of rectal cancers located in the distal rectum presents a unique challenge for surgeons as it is anatomically unfavorable and technically difficult to access. Over the course of the 20th century, novel techniques contributed to the improvement of rectal cancer management and led to improved quality of life for patients following surgical resection. In this article, we explore the background of rectal surgery techniques, which have progressed from abdominal perineal resection to transanal abdominal transanal proctosigmoidectomy, transanal total mesorectal excision (taTME), and ultimately minimally invasive transanal sphincter preserving techniques utilizing single port robotic technology (SPr taTME). In the first clinical experience with the DaVinci SP robot in the United States, we are finding many advantages of this new platform in transanal surgery. The SP offers superior image quality with 3D view, wristed instruments facilitating ergonomics, and superior surgical precision.

Keywords: Transanal abdominal transanal, transanal minimally invasive surgery, da Vinci single-port robot, transanal, rectal cancer

INTRODUCTION

“An invention has to make sense in the world it finishes in, not in the world it started.” Tim O’Reilly.

For a large portion of the 20th century, low-lying rectal cancers were commonly treated by performing an abdominoperineal resection (APR), first reported by Miles^[1] in 1908 [Figure 1]. While the APR is oncologically effective, it distinctly alters the gastrointestinal anatomy and leaves the patient with a permanent colostomy. This procedure was adopted as standard treatment for rectal cancer for much of the



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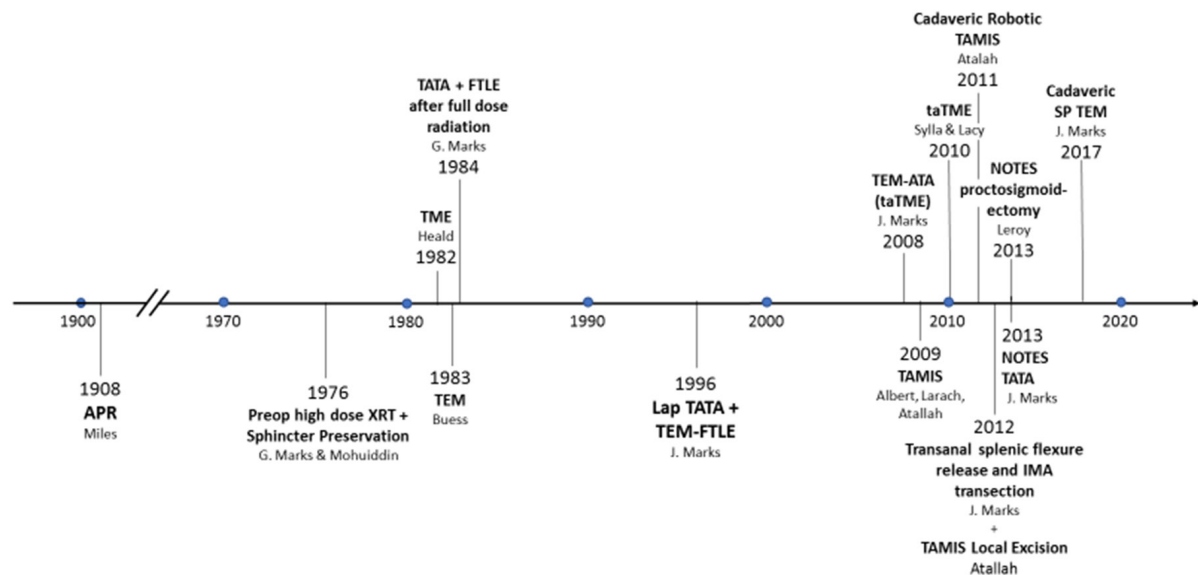


Figure 1. Timeline depicting the evolution of rectal cancer. APR: abdominoperineal resection; TEM: transanal endoscopic microsurgical; TME: total mesorectal excision; TATA: transanal abdominal transanal; FTLE: full thickness local excision; SP: single port; NOTES: natural orifice transluminal endoscopic surgery; TAMIS: transanal minimally invasive surgery; taTME: transanal total mesorectal excision; XRT: radiation; ATA: abdominal transanal; IMA: inferior mesenteric artery

century. However, local recurrence (LR) rates of 20%-40% in the 1970s and 1980s and a desire to extend sphincter preservation led to critical advances in rectal cancer management^[2].

Improved operative approaches and high dose preoperative radiation were shown to reduce the rates of LR in rectal cancers over the latter half of the 20th century^[3]. In 1982, Heald and Ryall^[4] sharpened the focus on precision and proper surgical technique by performing meticulous dissection of the mesorectum and formulating the term total mesorectal excision (TME). TME has since become a fundamental principle in rectal cancer surgery and proved to reduce local recurrence rates.

Prior to this, in 1976, Mohiuddin *et al.*^[5] embarked upon the first program in the world that offered sphincter preservation following high dose radiation therapy in the preoperative setting. It was quickly realized that the irradiated rectal cancer was often so downstaged that sphincter preservation could be expanded. A challenge existed in the diminished size, making the tumor difficult to reliably palpate intraoperatively, hence leading to difficult determination of the distal tumor margin. To address these two problems of extending sphincter preservation and assuring an adequate distal margin, a new operative technique was conceived. In 1984, Marks *et al.*^[6] developed the transanal abdominal transanal (TATA) proctosigmoidectomy with coloanal anastomosis. The operation commences by incising the rectum in a full thickness fashion at the level of the dentate line and continuing the dissection cephalad. The rectal lumen is oversewn in a watertight fashion. In this manner, a known distal margin to the tumor is established and a total proctosigmoidectomy is then accomplished from an abdominal approach. This resection is followed by a direct coloanal anastomosis using healthy, non-radiated tissue from the descending colon, and avoids the need for a permanent colostomy. Contrary to the standard treatment of cancers in the distal third of the rectum, which requires navigation through the narrow confines of the deep pelvis, the TATA procedure avoids the need to apply a stapler from above. An underemphasized benefit of this approach is that the most difficult part of the operation is carried out transanally, at the beginning of the operation. In addition to preserving sphincter function, Marks *et al.*^[7] was able to reduce the local recurrence rate to 9% in a time where local recurrence was reported to be 25%. The TATA procedure was shown to provide an oncologically safe sphincter preserving procedure for patients that otherwise would have received an APR^[7].

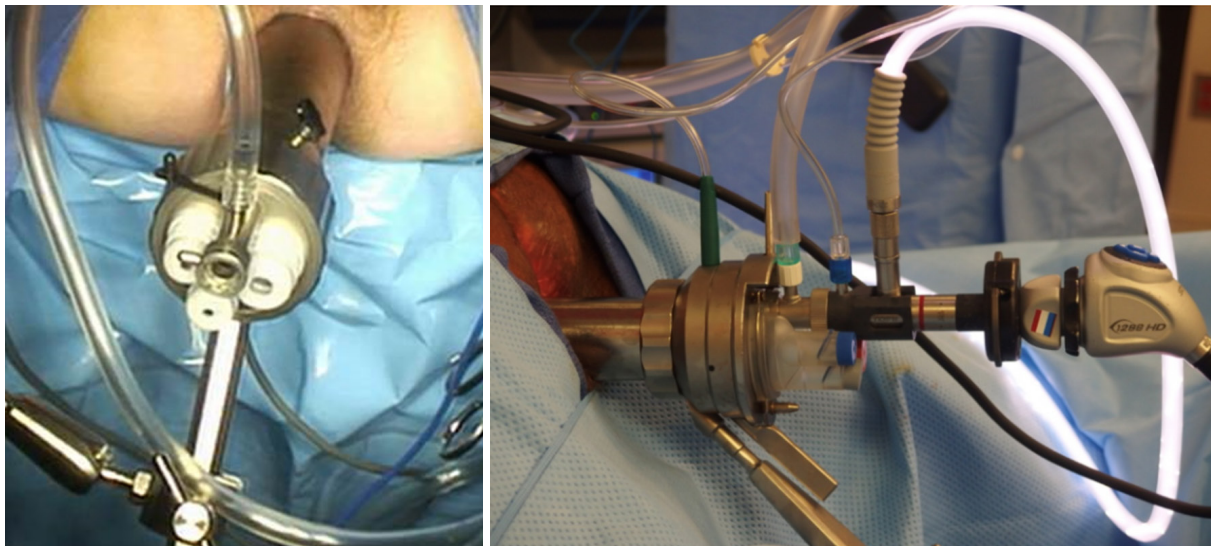


Figure 2. Transanal endoscopic microsurgical platform inserted transanally

In 1984, following the conception of the TATA, Kosinski *et al.*^[8] ventured to perform a full thickness local excision (FTLE) of a distal rectal cancer after full-dose radiation. This early experience demonstrated that local excision after neoadjuvant radiation could not only be performed successfully, but also safely with a low rate of local recurrence. This approach was slowly adopted due to the engrained beliefs that operating in an irradiated field leads to poor healing and high leak rates. However, due to superior oncological outcomes, the advantages of multimodal therapy were ultimately accepted, and neoadjuvant therapy became a standard practice in locally advanced cancers.

As is often the case with emerging technologies, the advent of minimally invasive surgery brought about further advancement in the surgical treatment of rectal cancer. Prior to the first laparoscopic abdominal procedure, in 1983, Dr. Buess^[9] developed the transanal endoscopic microsurgical (TEM) platform for resection of rectal polyps and early stage cancer [Figure 2]^[10]. This technique used rigid laparoscopic instruments via a single transanal port to provide superior reach and exposure to rectal pathology that limited prior open transanal approaches. Dr. John Marks furthered this technique in 1996 when he performed a transanal endoscopic microsurgery full thickness local excision (TEM-FTLE) following neoadjuvant high-dose radiation. Later, in 2008, he used the TEM platform to perform the first transanal total mesorectal excision, which he termed TEM-ATA.

TEM was the first example of natural orifice transluminal endoscopic surgery (NOTES), which led to many advancements in minimally invasive surgery and specifically rectal surgery. In 2009, Atallah *et al.*^[11] developed the transanal minimally invasive surgery (TAMIS) platform [Figure 3]. While similar to the TEM technique, TAMIS allowed surgeons to perform radical rectal excisions via a more accessible single incision port as opposed to the rigid TEM proctoscope. Lacy *et al.*^[12] further facilitated transanal access to rectal pathology by conducting an IRB-approved study of the single incision laparoscopic surgery platform. They are to be credited with popularizing transanal total mesorectal excision (taTME).

Both Drs. John Marks and Joel Leroy can be recognized for pushing the limits of transanal surgery using the TAMIS technique. In 2012, Dr. Marks accomplished the first transanal splenic flexure release and IMA transection. In 2013, Leroy *et al.*^[13] performed the first “pure” NOTES proctosigmoidectomy, which he termed peri-rectal oncologic gateway for retroperitoneal endoscopic single site surgery. In the same year, the first NOTES TATA was demonstrated by Marks *et al.*^[14], who later published a dynamic manuscript



Figure 3. Transanal minimally invasive surgery platform inserted transanally

outlining the critical views for pure NOTES proctosigmoidectomy via TAMIS. While these advancements highlight what can be achieved transanally by highly experienced surgeons with single port laparoscopy, the ergonomics and technical challenges of these approaches resulted in limited adoption of these techniques.

As robotic surgery emerged, Atallah *et al.*^[15,16] described the first robotic TAMIS in 2011 using the da Vinci Si robot on a cadaveric model and later performed the first local excision of rectal cancer on a live patient in 2012. Subsequent to this, several institutions have reported on their experience with robotic TAMIS. The advantages reported are superior 3D view, wristed instruments, better ergonomics, and superior precision. Despite these benefits, the multi-arm robot was found to be ill-suited for single port surgery. External arm clashes and internal conflicts have relegated this approach to an interesting novelty.

With the clinical introduction of the da Vinci Single Port (SP) robot, many of these hurdles of robotic single port surgery have been addressed, employing this technology in the next generation of robotic TAMIS (rTAMIS). The da Vinci SP platform is a single arm single port system that is ideal for rectal procedures [Figure 4]. The SP system includes three 6-mm jointed and wristed instruments and the first da Vinci jointed 3D camera [Figures 5 and 6]. This facilitates viewing and operating on all quadrants of the rectum without repositioning the patient. The hologram of instrument position seen on the SP screen allows the surgeon to better avoid instrument collision and permits superior retraction. Current instruments available for the SP robotic system include: needle driver, cadere forceps, round tooth retractor, clip applier, monopolar scissors, monopolar hook and spatula tip cautery, and both Maryland and fenestrated bipolar forceps. To date, there is no SP vessel sealer, suction, or stapler. These represent significant drawbacks that will likely be added in the near future.

In a cadaveric feasibility study, the SP robot was shown to be a realistic platform for the future of endoluminal surgery. As reported in a manuscript published in 2017, Marks *et al.*^[17] performed 12 local excision procedures (SPr TAMIS) with no fragmentation of the specimen and negative margins. In January 2020, the first clinical experience performing a single-port left colectomy using the SP robot (SPr SILS left colectomy) was described^[18]. Relative ease and comfort were noted with this novel operative platform with minimal physical or mental fatigue to the surgeon. In an FDA regulated feasibility study, the use of the SP robot was expanded to perform transanal TME dissections. Building on prior laparoscopic transanal total mesorectal excision experiences, Dr. Marks began utilizing the SP robot in total transanal TME procedures, including transanal splenic flexure release and high ligation of the IMA. The results of these experiences have yet to be published. With these advances, the SP robot demonstrates significant surgical milestones



Figure 4. Single port robotic platform



Figure 5. Angulation of single port robotic instruments employed through the single port trocar

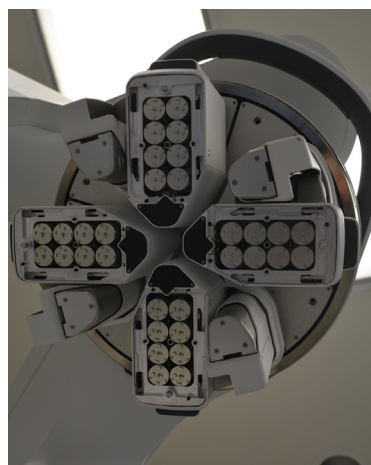


Figure 6. Single port instrument insertion platform

in the field of transanal and other natural orifice surgery. From APR, to TEM and NOTES, to TAMIS and the advent of SP robotic transanal surgery, technological advances are constantly providing surgical and oncological advantages in the treatment of rectal cancer.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study: Kunkel E, Martin C, Agarwal S, Marks JH

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

E Kunkel, C Martin, S Agarwal and H Schoonyoung have no conflicts of interest to disclose. Dr. John Marks is engaged with Intuitive Surgical in a consultative fashion to develop the safe application of the SP robot. This has entailed detailed conversation as well as cadaver work utilizing a robotic protocol. He has been financially compensated for this work.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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MIS AI - artificial intelligence application in minimally invasive surgery

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Abstract

This chapter is devoted towards analyzing the progress and barriers to the development of artificial intelligence (AI) and medical robotics in minimally-invasive surgery. The less invasive the surgical intervention and the further the surgeon is from the operating table, the greater the roles of decision support systems (AI) and performance of specific tasks (by medical robots).

Keywords: Artificial intelligence, medical robots, mini-invasive surgery

INTRODUCTION

The robot is not a machine but an IT device that creates a great opportunity for the integration of the entire diagnostic system with the operator^[1]. “The future of technology and medicine is not in the blood and bowels at all, but in bits and bytes”^[2]. This is how Prof. Richard Satava, a surgeon from the University of Washington who led the first surgical robot project funded by the DARPA (US Defense Advanced Research Projects Agency), summarizes his many years of experience and visions for the future of surgery.

Surgery is a specific type of medical activity that uses direct physical methods of intervention in a body area damaged by illness or injury. Precise movements by the surgeon requires proper planning and control. Correct positioning and functioning of the tools requires good image quality and all current information from the operating field.



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Information is processed during the work of the surgeon or via remote control. The effect of the operation (achievement of the assumed goal) should be measurable and verifiable. Only then can it be used to develop the standard of the service performed, lead to automation and the independence of medical robots in the future.

The operation is part of the patient's treatment strategy. Surgical planning provides a possible and effective approach to use available resources (tools, team, equipment, biological or artificial materials) for the creation of a specific impact (using physical, chemical, biological phenomena) on biological tissues.

The surgeon uses both conditioning and coordination of motor skills to process information during the operation. The information obtained in the process of education and practice (optimized through knowledge and experience), and diagnosis are provided by human senses.

INTELLIGENCE

Intelligence is the ability of humans to perceive, analyze and adapt to changes in the environment. The ability to understand, learn and use knowledge and skills in different situations, intelligence is a feature of the mind that is responsible for reacting appropriately to and solving problems using: understanding of words, verbal fluency, numerical and spatial abilities, reasoning, memory and perception.

The space we live in is a space of information. For the doctor, the surgical field is also a space of information. If we manage to digitize all images, physicochemical data, and the patient's medical history in the evaluation process, we can analyze this collection of information. If we can digitally describe the treatment methods (the impact of drugs and surgical operations), we can then build a treatment model for a given patient.

Intelligence - both natural and artificial - will be used to optimize the decision-making process for patients in this multidimensional information space.

Artificial intelligence

In my opinion, artificial intelligence is a part of robotics. The source of the word robot is associated with the figure of an artificial man introduced by the Czech Karel Čapek 100 years ago - R.U.R. Rossumovi Univerzální Roboti (Rossum's Universal Robots). Robotics is a technical discipline, which deals with the synthesis of certain human functions through the use of mechanisms, sensors, executive assemblies and computers. Because humans have a brain, artificial intelligence is an integral part of robotics.

Generally, artificial intelligence was created for communication between machinery and human intelligence. The robot is an artificial man or part of a humanoid robot, artificial organs or artificial intelligence.

Kevin Warwick, known as the first human cyborg (after implanting an electronic interface) claims^[3] that "where a brain is involved it must be seen as part of an overall system - adapting to the system's needs". Warwick is a pioneer in studying the connection between the biological body and the robot.

Robots

The traditional definition of robot means artificial man. From this point of view, the robot should have the ability to move (to perform mechanical work) and make decisions based on information provided by its senses (intelligence). While many animals have these features as well, human beings also have, apart from intelligence (which determines the correct response to stimuli), a reasoning mind, i.e., the ability to use abstract objects (theory) for calculation, objectification, prevention, and planning. Man also has consciousness.

The number of people in the world is approaching 8 billion and 3 million robots help them in industries, factories and services. According to the IFR^[4] there are 85 and 114 robots per 10,000 employees in the world and Europe respectively. Websites providing various current data measurements for humanity (such as <https://www.worldometers.info/pl/>) may soon provide information about robots supporting people at work and at home too.

Robots were introduced to factories when there were not enough people to produce the right number of products. And how is it with the surgeons? Accordingly^[5], “an insufficient client surgical workforce is a major barrier to safe surgical care for billions of people worldwide”. Worldwide, there are an estimated 1,112,727 specialist surgeons and 550,134 anesthesiologists. Low- and lower-middle income countries, representing 48% of the global population, comprise about 20% of this workforce. In terms of density, low-income countries have 0.7 providers per 100,000 population, compared with 5.5 in lower-middle income countries and 56.9 in high-income countries^[6].

I believe that many individuals, like me, believe that it is our duty to reduce these differences in access to a good level of medical services. Of course, the biggest role here is in education and investment but perhaps progress in the use of artificial intelligence (AI) in medicine (that is the dissemination of the standard) will provide a real chance to reverse this catastrophic trend of ever-growing disparity in access.

How many operations are performed in the world? Depending on the definition used and access to data, at least 10 million different types of operations are performed each year^[7] and this number can even go up to 300 million^[8]. Based on available data, an estimation of the global volume of surgery using a modeling strategy suggests that “We have estimated that the global volume of major surgery in 2004 was between 187.2 and 281.2 million cases per year, which has substantial implications for public-health planning.”^[9]. The authors’ findings suggest that surgery now occurs at a tremendous volume worldwide, in both rich and poor settings. This unprecedented worldwide growth in surgery shows a great need for public-health efforts to improve the monitoring, safety, and availability of surgical services, especially in view of their high risk and expense^[9].

It is important yet difficult to estimate the real number of operations. There are certainly about 300 million if the authors calculate^[9] based on one operated person per 25 living people.

What about standards? How do you count and oversee it? From these examples, we can see that one of the needs that can be met by digital monitoring and AI methods is supervision and access to current data and to analyze them.

Let’s return to the robots. Just as robots solved the problem of mass production, perhaps they will allow the dissemination of uniform standards in surgery. They will facilitate access to good medical services. For now, however, while robots increase precision for some medical tasks, they are very expensive; surgeons are helped by about 5000 robots. Every year, almost 1 million minimally-invasive operations using da Vinci robots are performed^[10]. But these are telemanipulators and every movement of the tool and all decisions are still made by the operator. In addition, thousands of diagnostic robots perform tasks semi-automatically.

Robot control consists of perception, data processing and action. For robots to make a decision, it will need to have access to information and the ability to analyze it. Having information reduces the uncertainty (indeterminacy) of objects or relationships between objects, and allows recognition of the state of the system. Sensors are responsible for obtaining information about the environment and the current state (position) of the robot’s components and its system. An important element of service robot control systems is the ability to process video information received from the robot’s environment.

Like humans, the knowledge and skills of robots result from education, experience and usable memory. As with human verification, optimization must be associated with the elimination of wrong decisions and deeds. AI robots can get knowledge from people - this is the first level of learning in robots. If we pass on a collection of information about how it is or how we think it is, then the robot will make decisions that are perhaps burdened with our mistakes. If we teach the robot to read information (measurable data) from sensors and provide algorithms for the formation of correct decisions based on this information, we will achieve an automated device. If we allow it to modify decisions and actions and assess their effects, we will have a self-learning system that can make decisions different from those that we consider as appropriate. Many of us have already been refused a loan in a bank on a similar basis. But, if we give the robot design features based on human, but with additional motion capabilities, we can achieve much better “manual” function than humans. If we give the robot tools and greater efficiency and accessibility to the areas of the human body that we operate on, tissues, cells or genes - then we get a surgical robot with practical skills that are not accessible by humans.

Robots (Cobots) interacting with people change the way many professions perform. Robots create the possibility of standardization and constant improvement of quality through learning (AI) and communication with a professional information network (professional databases and management systems) as well as with other medical devices (diagnostic, therapeutic, rehabilitation), and also elements of hospital infrastructure.

Why do we need artificial intelligence in mini-invasive surgery?

Man is only as good and useful as his senses allow. Similarly, a robot that is created in the image of a human being, by definition, cannot do more advanced work if it has a limited number of sensors, or lacks the processing of sufficient information to make the right decisions. After all, robots are all about doing work and in surgery, it is all about decision-making and mechanical work.

Suppose, in favor of these considerations, that (1) intelligence is a certain ability to make decisions independently, based on the analysis of signals (senses) that determine the state of the environment and the possibility of the subject's impact (the surgeon using his tools) based on basic knowledge of the entire system (memory) that was developed during the learning process (system evolution by verification and optimization of goal achievement); (2) surgery is an action of removing the effects of a disease, birth defects or injury (bodily injury due to various reasons), the action of mechanically modifying the structure of tissues and organs (surgery) and/or the introduction of natural or artificial elements to replace parts of the body or supporting proper bodily functions (passive or active, artificial and biotechnological implants - e.g., stem cells and devices for physical, and mechanical, electrical or chemical stimulation of tissues).

We treat the human body as a biological, physical, chemical and biocybernetic (IT) system. Why is artificial intelligence important in medicine? First of all, decision-making plays a key role in every medical process. Based on the analysis of diagnostic data and medical history, the treatment process begins and its effectiveness is verified in the next step. The basis of evolutionary progress is the process of learning, remembering and disseminating standards. In medicine, the possibility of direct proof is very rare. Usually, the number of unknowns does not allow building full cause-and-effect knowledge to define the possibilities of our therapeutic effects. We do not have the theory of the whole organism, nor do we have the theory of one or another disease, similar to the theories of physics. That is why the doctor makes decisions based on random diagnostic data (and not a full description of the whole organism) and in the treatment specialties such as surgery, the role of sensory assessment (sight, touch, smell, hearing) and manual skills increases (due to the speed of action and real risk).

If, however, we assume that we would like to operate in a place where our intervention is necessary by methods that reduce the risk of damage to healthy tissues as much as possible, it means the loss of the ability to freely view and touch the tissue, the inability to directly insert our hands in the place of surgery. This is the current MIS dilemma. Is this beneficial for the patient? Can a surgeon possibly do this?

This is a challenge for creating new tools and both artificial intelligence and robots are one of them.

In the mathematical context, artificial intelligence is not an ordinary algorithm, which is a mathematical record of a cause and effect relationship, but a system based on say, neural networks that map the way of building memory pathways in the human brain - i.e., a decision system based on knowledge and experience, similar to the learning process. We do not quite know why such a decision is made but we are sure that the process of system optimization achieved the appropriate level of excellence. This is interesting from the point of view of applying AI successfully in medicine, as it proves the existence of an art factor in the craft of the doctor. You cannot replace a doctor with an automatic machine, i.e., a simple machine. Algorithms alone are likely not enough. There must be artificial intelligence in the decision making process and the robot in execution.

In medicine, artificial intelligence can definitely play a positive role in developing strategies and solutions for operations.

The word “strategy” comes from the Greek words *stratós* - army, army, and *ágein* - to command. Carl von Clausewitz defined that strategy is the science of using battles for war purposes. Strategy is not theoretical planning, but it is very close to action, modified by a steady flow of information.

The word “tactics” comes from the Greek words *tássein*, meaning *táttein* stack, organize, arrange. The commander creates and effectively uses the elemental system to combat factors such as destruction, movement and information. Isn't it also the essence of surgical intervention?

Surgery is a special human activity related to complex actions for achieving specific purposes. The complexity of an action is the need to assess the condition of the starting issue and making decisions about the distributed action in time divided into roles of the members of a special team.

Operation is a part of the patient's treatment. The doctor develops a treatment strategy and tactics to define the next elements of the procedure. Operation planning includes defining the space and subject of the operation, choosing methods, materials and devices, program of using the operating and accompanying team, and finally, the choice of the sequence of treatments, activities, movements and the impact of tools in the space of operations. The way of conducting surgery significantly depends on the equipment available.

Planning and advisory systems - extended surgeon information space

The surgeon who operates in a less invasive way has impaired access to information from the patient's body, the surgical field. In the classic version of video-surgery, a very good quality image is obtained - enlarged with clear outlines of contours and colors. We can support this set of visual information by adding information obtained in the diagnostic and analytical process. The ways to visualize this additional information is a separate field of ergonomics, including virtual and augmented reality technology.

In my team, we have been developing the use of computer simulation of surgical operations and the use of physical modeling to improve the patient-specific decision making process for many years [Figure 1]. The skillful use of physicists' knowledge allows us to obtain information, e.g., what will be the flow in a given branch of the coronary vessels after performing a sequential or single bypass, what will be the flow, pressure, regurgitation after implantation of a given type of prosthesis, etc.

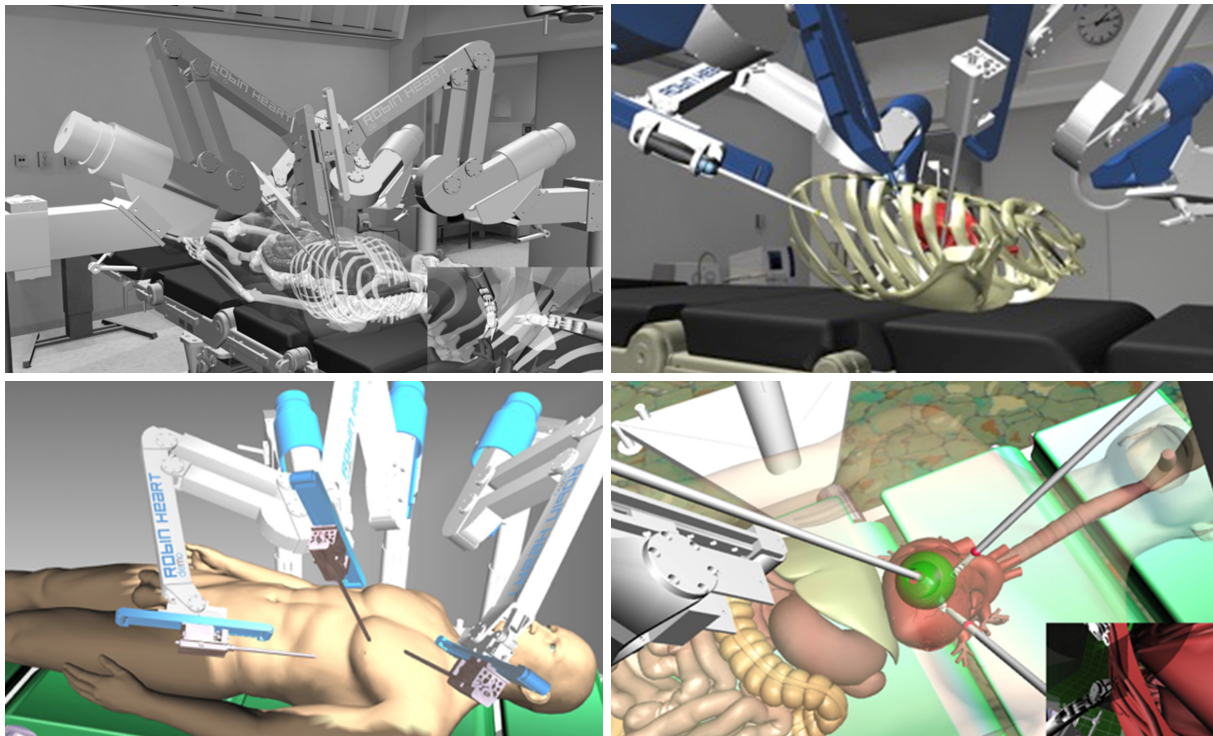


Figure 1. Virtual operating room made in FRK (in a team led by the author). It is used for planning operations using Robin Heart robots (examples are for heart surgery) and for testing robots (in the conceptual phase) and training surgeons. The developed program in virtual space technology was tested for use: (1) on a computer stand; (2) in the Robin Heart Shell 2 robot control console; (3) VR goggles (Oculus). The images below are examples of how to visualize simulated operations. The last image outlines the green work space available for the tool chosen by the surgeon

This means that we can enrich the image with prognostic information. Moreover, if we introduce an image analysis system of the operations performed by a surgeon, we can modify it to keep up with the effects of surgery. This is one of the aims of my research work in my Fundacja Rozwoju Kardiochirurgii (FRK) team.

However, this is still not putting AI into surgery. We have known for many years that we can use telemedicine systems for consulting and verification of the correctness of actions taken by a teacher surgeon who is located away from the operating room. The endoscopic track can be connected to a conference room where all participants can comment live on the operation which is performed in the hospital.

Telemedicine systems are successfully used when, for example, the surgeon has to undertake very little surgery, which is unusual for the practice, but in this way can use the advice directly from a more experienced specialist. In the information exchange system, we thus turn on the brain of another person who does not physically participate directly in the operation. However, if we imagine that we can model on-line surgery in a digital, computer (simulation) or physical (modeling) system and thus create possibilities for the history of operations by forecasting the results of subsequent steps taken by the doctor, we are then building a very advanced advisory system based on experimental facts (model). If the model is perfect (which is extremely difficult for physiological models) then we will get excellent advice. We can also base our advice for the surgeon on the analysis of real data, from real operations, i.e., Big Data analysis. In this way, we can build a very advanced advisory system based on medical facts. Clearly, this reasoning seeks to demonstrate that the combination of these approaches can be a breakthrough in the quality of advisory systems. The systems supporting the real surgeon while making decisions should graphically indicate the location, place of intervention and provide biological-chemical-physical data that is both current and forecasted based on a specific selection of tactics.

The decision-making system based on learning from patient databases, controlled and verified in every degree and iteration of its development, was developed by a group of outstanding professionals such as the well-known IBM Watson computer. Unfortunately, its skills, despite the enormous computing power, are still no better than a good doctor. Watson has now obtained approval for decisions regarding selected oncological diseases (by analyzing data from 200,000 correctly identified patients, he can make decisions with an accuracy of up to 97%, but only for a few diseases for now). However, Watson's difficulties indicate that entering into a live partnership during operations is still a long way off. Artificial intelligence can contribute to reducing errors, improving standards and the quality of performed operations, and increasing patient safety.

1. Indirectly, passively as the basis for the work of the advisory system when planning and performing operations.
2. Indirectly - as an element of surgical telemanipulator or mechatronic tools.
3. Directly - as the basis for the operation of an autonomous surgical robot.

Improving the decision making process is always associated with access to good, reliable and timely information. The surgeon manually performing a classic operation uses information from all his senses. The surgeon loses access to all this information by moving away from the patient during surgery. For instance, in endoscopic instruments with a distance of about half a meter and with telemanipulators over a distance of several meters or many kilometers.

Medical robots

The segment of medical robot systems (in market analyses) is divided into surgical robot systems, rehabilitation robots, non-invasive radio surgical robots, hospital and pharmacy robots and other medical robot systems. The following companies are present on the market: Intuitive Surgical, Inc. (USA), Stryker Corporation (USA), Mazor Robotics Ltd. (Israel), Hocoma AG (Switzerland), Hansen Medical Inc. (USA), Accuray Incorporated (USA), Omnicell, Inc. (USA), Ekso Bionics Holdings, Inc. (USA), ARxIUM (USA), Kirby Lester LLC (USA), Houston Medical Robotics (USA), Otto Bock Healthcare, Kinova robotics, Varian Medical Systems, Hocoma AG, Vecna Robotics, Globus Medical, IRobot Corporation, Titan Medical, Inc., and KB Medical SA.

Medical robotics has been the most successful so far in the field of surgical and rehabilitation robots (including exoskeletons). The robot leader on the soft tissue telemanipulator market is the da Vinci robot (Intuitive Surgical). Five thousand robots are currently used in approximately 1 million operations per year, mainly urological and gynecological. New surgical robots appear, e.g., ALF-X (USA), Titan (Canada), and in other areas such as Virtual Incision, TransEnterix (SurgiBot, Senhence robot-assisted surgical system), Corindus Vascular Robotics (cardiological robot, CorPath GRX) or Artas (robot platform for hair implantation) and endoscopic Monarch (Auris Health) and orthopedic Renaissance (Mazor Robotics). Medtronic introduced surgical HUGO (Einstein), and Medrobotics - FLEX - flexible endoscopic robotic tools.

Corindus, producer of CorPath GRX platform, received permission from the United States Food and Drug Administration (FDA) for the first automated robot movement called "Rotate on Retract (RoR)" in 2018^[11]. This is the first step towards introducing autonomous robot operations.

Telemanipulators allow remote-controlled operations from different distances. However, there is a distance-dependent delay in transmission of operation images to the surgeon that can be dangerous. Most researchers consider 300 ms as the limit in delay time^[12]. The implementation of 5G technology will overcome barriers and reduce the delay of 0.27 s to 0.01 s and also improve image quality^[13]. Worldwide, about 143 million surgical procedures are not performed due to the lack of knowledge of

specific procedures^[5]. Creating a network in which surgical operations are possible at a distance is a technological and political challenge. But only in this way we will then be able to solve the problem of “equal opportunities” for access to appropriate quality medical services.

Autonomy - independence of medical robots

For medical robots to play their role fully in the face of challenges from the growing needs of services, and the need to increase their quality, they must soon become independent. Stand-alone robots should operate in an information network, which allows access to all information needed to optimize operations in every situation. In history, medical robotics has already received support, several times, from technologies that were perfected for performing industrial tasks, aerospace or military projects. This time, the growing interest of the industry in co-robots - robots cooperating with employees on production lines - and strategies for the development of automation in the field of autonomous vehicles will give appropriate acceleration for the new projects of medical robots. Autonomous vehicles are currently being developed by technology giants such as Google, Apple, Tesla and Uber, a number of automotive companies including Mercedes, Volkswagen/Audi, BMW, General Motors, Volvo, Ford, a consortium of Renault-Nissan-Mitsubishi and Toyota, and companies producing computer components like Nvidia and Intel.

We probably will not make the mistake of systematizing the autonomous capabilities of medical robots based on the five-level classification of autonomous vehicles introduced by the SAE International (Society of Automotive Engineers) standardization organization. The autonomy of medical robots on a five-point scale (modeled on the SAE J3016 standard) though, with the lowest level, 0, is a lack of autonomy:

1. Level 1 is telemanipulation (remote control) with support. In this type of robots, some elements have been introduced to support operations automatically. It can be, for example, an emergency stop system for a robot in a hazardous situation. Surgical robots such as da Vinci and Robin Heart are currently in this group.
2. Level 2 represents robots with the option of partly automated work. A robot that can perform one of the tasks in an automated manner, e.g., tying a node or orientation of the cam-vision track to a tool.
3. Level 3 is highly automated work. The system moves independently in the work space and scope of tasks but is still able to assess the limits of its freedom. If it judges that the working conditions are outside the defined area, the operator must immediately take control of the robot. In the absence of such a reaction, the robot stops. Such robots are self-propelled robots for tele-presentation and so-called robotic nurses for communication and transport of various products and materials in hospitals.
4. Level 4 is fully automated work. The robot works independently but should still be supervised, e.g., by a doctor, rescuer or physiotherapist. An example of a vehicle - a robot - included in this level is the autonomous Volvo XC90 used in Uber tests (in the vehicle there is a driver - a human verification element that can take over steering, after warnings from the control system). Such machines are currently computer tomography or robotic radio-surgical knives that move and operate in accordance with the planned trajectory and tasks specified before the surgery.
5. Level 5 means a robot working fully autonomously. The medical robot works independently, sharing space with the patient and medical staff, makes independent decisions and performs tasks provided for in its specialization. The robot has no tele-manipulation system. An example is the city car prototype developed by Google, Waymo Firefly i.e., a car without a manual control system, including the steering wheel, gear lever or pedals. There are currently no such medical robots.

FRK OWN EXPERIENCE

The Professor Zbigniew Religa Foundation for Cardiac Surgery Development in Zabrze is a pioneer in Poland in the field of medical robots for heart prostheses and surgery. Robin Heart is the name of the whole family of Polish surgical robots intended for heart surgery (also soft tissue) and for now, consists of: Robin Heart 0, Robin Heart 1 and Robin Heart 2 created in 2000-2003; Robin Heart Vision in 2007-

2008 (for video surgery, one arm robot); modular robot Robin Heart mc² from 2009; TeleRobin form 2014 (new solution of the tool platform), followed by subsequent versions of the video surgery robot; ultra light Pelikan and Robin Heart PortVisionAble in the preclinical version. At that time, Robin Heart mc² was the largest surgical robot in the world. It consists of three arms: two arms working as an assistant and a middle arm equipped with a tool platform (two tools of the main surgeon and vision endoscope). Robin Heart Shell console is equipped with a 3D monitor and an additional touch screen to change control parameters (tremor removal or motion scaling) and an advisory system (that shows the necessary diagnostic data as well as the results of planning and simulating operations). Robin Heart mc² is a modular robot with the tools, which can be quickly removed from the robot arm and used as manually controlled mechatronic tools. The Robin Heart system was tested in animal experiments at the Experimental Medicine Center of the Medical University of Silesia in 2009-2010 (gallbladder surgery, coronary artery bypass grafting and heart valve repair)^[14].

The surgery planning system is based on the use of an original virtual operating room. The simulation of operations was prepared by the team at the Biocybernetics Laboratory to allow the introduction of physical features (pressure and blood flow) to hemodynamic models of heart surgery. The Polish team is preparing to introduce robots to the market, for clinical implementation. Elements of artificial intelligence will, in the first version, be applied to the advisory program presented online when controlling the robot from the Robin Heart Shell console. Subsequently, semi-automatically performed tasks and selected elements of the procedure (e.g., tying the knot while sewing or cutting a hole of a certain shape) will be introduced. The key to introducing AI to surgical robotics are sensors, image analysis and processor speed. We believe that in the future, these robots will be completely independent.

Purposes and necessary conditions for using AI in MIS:

1. In advisory programs and planning support systems, AI serves as a method of linking the current situation during a surgical operation with the results obtained earlier in clinics (if they are digitized, i.e. form elements of the Big Data base) or obtained from physical modeling, computer simulations or the use of models theoretical in calculations.
2. In mechatronic surgical instruments, if the instruments are equipped with sensors (determining the features of local surgical intervention), soft & hardware to understand what specific signals mean for the task being performed and monitors presenting data to the surgeon online.
3. In surgical telemanipulators, if robots are equipped with sensors (determining the features of local surgical intervention and force feedback), AI can be used in a system of supervision and control of performed surgical tasks and creating the basis for working with the image of augmented reality technology. Innovative surgical instruments equipped with force sensors and/or performing semi-automatic tasks (such as sewing) play a key role in this process.
4. In independent surgical robots, if robots can on-line process information available from sensors, their own computer and cloud database, creating information loop containing physical/chemical/biological data, data from memory resources regarding the practice and theory of selected surgical procedures (imitating the medical knowledge of the surgeon), as a element of central decision making system (AI) and the implementation of surgical tasks.

Of course, we must remember that surgery is collective work, and the team consists of an anesthesiologist and many other specialties including nursing and technical support. There is also information about robots being developed to replace the work of people from the team accompanying the surgeon. It is possible that the entire operation will be robotic. Contrary to common belief, this is not an impossible task, if we were to seriously consider plans to build settlements on the moon or Mars by comparison.

In my Robin Heart Team in Zabrze, we conduct research and design work, and we build and test mechatronic robots and tools. The FRK Biocybernetics Laboratory is also a pioneer in the field of



Figure 2. Selected elements of the history of the Robin Heart surgical robot, which was created in the FRK in a team led by the author

simulation and modeling of heart surgery by creating data on the hemodynamic effects of surgery performed in a given way^[15-19]. Figure 2 shows examples that demonstrate the achievements of the FRK within the scope of 1-3 of the AI implementation plan for MIS.

AI and ethics

Text based on^[20] The Ethics of Artificial Organs in Implant Expert by Zbigniew Nawrat, with permission.

I believe ethics to be the art of making the right choices. And modern medicine, with its new medical techniques, healthcare systems and financing schemes, creates a completely new area of insecurity in this regard. For ages, philosophers have been analyzing issues connected with man-vs.-man and man-vs.-the world relations in order to help us comprehend the reality and find the correct conduct.

The term “ethics” comes from the Greek word *ethicos*, meaning a way of conduct accepted in society, a conduct according to the legal character (*ethoscharacter*). Today, “ethics” is colloquially understood as “morality”, although the Latin word *moralis* denotes judgement of the appropriateness of a given action, more so than a person’s character.

The use of AI and robotics in the treatment process facilitates remote medical care, consultations and the monitoring of a patient’s condition. It is therefore a chance for greater availability and the quality of medical services. AI and robots are a breakthrough in infrastructure, organization of the operating theatre, and in the specialist training of surgeons. But how do we evaluate a wrong decision or action of a doctor from a distance? How do we divide the responsibility for mistakes of remote robotic devices? The access to information depends on technical resources such as software, *etc.* Therefore, the final effect is influenced by a number of people - engineers, administrators and economists, *etc.* as well as fortuitous events. Ethics and morality assume human-to-human contact. Our conscience and empathy work differently in the absence of a direct connection between our actions and their effect on others.

The technological progress in biomedical engineering and regenerative medicine constitute the basis for innovative artificial organs which are adequately small, efficient, durable and energetically and mechanically functional.

A new generation of Micro-Electro-Mechanical Systems is entering medicine. The fast development of bioelectromechanical microsystems (bioMEMS), micropumps and bioinformatics has created new possibilities such as the “lab on a chip” micro-laboratory, which are revolutionizing diagnostics and therapy.

In the near future, technical devices, entirely artificial organs and robots will be used to secure tissue therapy and genetic therapy. The integration of engineering and biology is a fact.

Thanks to bioengineering and medicine, today we can influence the survival of certain individuals and entire groups of patients.

With the harmonious development of technical and biological sciences and their reasonable implementation, and the quality of life on Earth.

Artificial intelligence is part of this evolution. Since it is an element of management at the level of organs and organisms, such medical procedures on the body will require hospital or state management and we must introduce ethical criteria agreed by all people.

AI - towards greater efficiency, permanent improvement and credibility

The popularization of telecommunications and the Internet is a good example of democratization and equal access to human achievements. We all can, rich or poor, in America and Africa, in the city or in the countryside, have access to Google search engines and data collected in public libraries around the world. Just as we can check the weather, because we supervise data from various places around the world, we will be able to supervise our body condition - as long as we are able to collect relevant data from all organs of our body. This is the future of "lab on chip". But today, by collecting data from our health records, we can make better decisions about caring for our health. By analyzing diagnostic data, we can make better decisions about invasive medical intervention, but for now the mediator is a person - the doctor. Soon, however, we will be giving the next decision to robots (communication of devices without the mediation of a human as a decision maker) and no one is surprised today when the door in front of us opens automatically. I am convinced that it will be a good time for humans, their health and safety, and we will be able to develop our skills and activities in completely new directions.

In the case of legal responsibility, it is worth looking for an analogy to obtain adequate social support. Computer advisory programs, decision systems and autonomous robots operate either on 1) the basis of transparent algorithms linking the cause and observation with effect and decision, or 2) on the basis of machine and deep learning - AI. In the former, we can conclude that the rules of operation are legible to the professional user (e.g., doctor) and the beneficiary, the client (e.g., patient) and the right of informed consent can be introduced. If the system of performing tasks, producing a council or a specific medical act does not take into account the absolute safety of the patient but other factors like economics (e.g., whether the client has paid for the service or is insured) then it is a matter of rules that we know perfectly well from the operation of health services. If someone introduces a virus and changes the system in a way that poses a danger, we already have (?) ways that are working such as criminal law. However, if the system works on the basis of machine learning, it is a completely new type of relationship where the client is the robot. First, we have an analogy: generally, neither the teacher nor the professor or the father is responsible for the student's deeds although in each case they are in a teacher-student relationship. Similar to the teaching process of students by introducing a different learning system, we can obtain a good or bad AI program/robot. It can make right or wrong decisions based on the data and save or kill a patient. No one is able to check how it works without starting the system because there are no readable rules inside. Just like looking into the human brain, by itself it is difficult (?) to assess whether it belongs to a surgeon or a shopkeeper. Our only option, as well as the system of training doctors and their acquisition of specialties entitling practice of the profession, will be to test and assess the effectiveness of autonomous robots, and to make sure that no computer virus destroys learning outcomes! Then we free robots from responsibility, just as we free specialists from responsibility, believing that he does the best, in a world where the end result is never obvious and certain. Just like man, AI does not have all the data to "solve the equation of life" for the patient.

The robot has the right to break. It is not allowed to make a move without the consent of the operator. During power outages and other problems, it must be possible to remove the tools from the patient by means of a medical team. I myself was a witness to this in the early phase of implementation of the da Vinci robot: during an on-line operation for its participants at a conference in Leipzig, one of the arms of the da Vinci robot stopped listening to the surgeon's hand. Our excellent colleague continued his classic surgery without squinting. Experience and skills, reason and knowledge always promote happiness.

Excessive optimism related to the shorter path of gaining experience in robotic operations was the reason for many crisis situations and simple mistakes. The patient's death during the first mitral valve surgery with a robot in the UK was resounding. The surgeon lost visibility after damage to the aorta which flooded the camera. The patient died. "An inquest has heard how Sukumaran Nair lobbied to be allowed to perform a mitral valve repair using a state-of-the art Da Vinci robot, despite performing slowly during non-robotic operations and passing up opportunities to practice on the machine"^[21].

The da Vinci robot is a telemanipulator. The control system allows you to direct the movement of the tools using the movement of the hand of the surgeon sitting at the console. Sometimes the control signal transmission system (e.g., cable damage) or movement mechanism (e.g., mechanical damage) fails. Here is an example of the description of such an event noted by the FDA: "System error codes #20009 and #21009 appear when the da Vinci safety system determines a differential change in the angular position of one or more robotic joints on the specified manipulator, as measured by that joint's primary control sensor encoder and the secondary sensor potentiometer. The system alarm system generated fault code-functioned as designed and there was no injury to the pt. Upon determining this condition, the safety system put da vinci in a "recoverable safe state"^[22].

The FDA has an online database MAUDE (Manufacturer and User Device Experience) filed by manufacturers, health care facilities, patients and lawyer, and includes thousands of incidents (ranging from error code bugs to patient deaths) related to the use of various da Vinci robotic systems. In Homa Alemzadeh and colleagues "A Retrospective Study of 14 Years of FDA Data" summarized that between 2000 and 2013, a total of 144 deaths, 1391 patient injuries and 8061 device malfunctions were reported with robotic surgery (10,624 reports at a time when 1.75 million robotic procedures were performed). Device and instrument malfunctions, such as falling of burnt/broken pieces of instruments into the patient (14.7%), electrical arcing of instruments (10.5%), unintended operation of instruments (8.6%), system errors (5%), and video/imaging problems (2.6%), constituted a major part of the reports. Device malfunctions impacted patients in terms of injuries or procedure interruptions. In 1104 (10.4%) of all the events, the procedure was interrupted to restart the system (3.1%), convert the procedure to non-robotic techniques (7.3%), or to reschedule it (2.5%)^[23].

According to the FDA database, in the 5-year period ending on Aug 31, 2017, the agency received 30 reports of incidents in which the patient died in connection with surgery using the da Vinci system. The system did not necessarily cause those deaths, but they occurred after or during surgery in which surgeons used the system. During the same time period, the FDA received 282 reports involving patient injury.

Experts say that the main contributing factors to robotic surgery adverse-event reports are: device failure (30%), device operational/setup (25%), user error (20%), inadequate training (7%), maintenance issue (7%) and others (11%)^[24].

That's all for the manipulator. The equipment or person may fail. But if we were to have an autonomous robot, who or what will be considered guilty? Who will be responsible for the wrong diagnosis or bad result from surgery? Engineer, constructor, director (owner) of the hospital, the supervising doctor or

even, the economist? Or maybe a lawyer? Or perhaps the family/patient agreeing to use it? Again, looking at the successes and progress (including failures) of the development of autonomous vehicles, we see that the solution will not be easy. It will probably be different for different treatments and activities, depending on the patient's balance of risk and chance. Just as we agree, as road users, that the fire brigade should not follow common traffic rules (as a delaying factor) in order to rescue people. But before we worry about how to solve this problem for interventional medicine, we need to solve this problem for better-developed artificial intelligence applications in diagnostics. Already today, there are companies, for example, which diagnose on the basis of an image analysis of the cornea of the eye and bravely take full responsibility for the opinions issued. Of course, none of these areas of diagnostic imaging (using humans or robots) is 100% correct.

CONCLUSION

There is one more important reason why we have to rely on artificial intelligence: human intelligence is decreasing. Humanity has reached a point where successive generations are becoming less and less intelligent. After analyzing over 730 thousand intelligence tests, Norwegian scientists^[25] found that, the average IQ in society is now statistically decreasing by 7 points for each generation since the 20th century.

I explain it this way. Increasingly, we are using memory and calculating and decision-making abilities in an easier world full of computers, search engines (Google), smartphones and smartwatches. Convenience comes at the expense of efficiency.

Since human intelligence is diminishing and sooner or later, artificial intelligence will be growing more, many scientists estimate that in twenty years, robots will have human level intelligence. Whether the performance efficiency then will be similar to that of the best surgeons is difficult to say but in general, mechanics does not develop as quickly as electronics. The art of robotics is based on an intelligent combination of mechanical work and information management obtained by sensors.

For now, information about the progress of AI in medicine is not as optimistic as we had expected. After all^[26], Medical AI, which pulled in \$1.6 billion in venture capital funding in the third quarter alone, is "nearly at the peak of inflated expectations". Even Topol, the author of "Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again", also acknowledges that many AI products are "little more than hot air".

As the summarized IBM Watson state of art now says^[27], "They've been trying to go into all sorts of things with mixed success and one of the most hopeful things was that they would be able to revolutionize medical care, health care. And it's not worked because they could look up symptoms of various diseases and they could look up cures for various diseases and they could look up medical articles. But they don't understand which are more meaningful than others, which medical articles are reasonable and which are bull and so a lot of doctors have become disillusioned with Watson. And a lot of hospitals have literally pulled the plug".

However, there are fields of medicine, e.g., dermatology^[28] and radiology, in which we are already successfully using expert programs. "The test, sold as IDx-DR, screens patients for diabetic retinopathy, a leading cause of blindness, and refers high-risk patients to eye specialists, who make a definitive diagnosis. IDx-DR is the first 'autonomous' AI product - one that can make a screening decision without a doctor. The company is now installing it in primary care clinics and grocery stores"^[26].

So why are the successes of artificial intelligence much better in image recognition? Why did deep learning methods and currently available computing power make AI practical and useful in medicine, now? The

expert systems (such as MYCIN for the recognition of pathogenic bacteria) were developed to solve medical diagnoses using rules from 50 years ago. For the operation of such a system, all facts and rules, as well as symptoms and histories of patients' diseases should be collected from specialists. Then, the software author needs to enter the data into the computer to conduct "reasoning in accordance with the laws of logic" and to constantly update the system with new data. These systems do not "scale out" and cannot succeed because of a high level of complication of a problem (e.g., starting in 1984 project CYC - sum of all data on human judgments). Only research on the human brain, discoveries explaining the actions of neurons (e.g., Alan Hodgkin, Andrew Huxley, Bernard Katz) and attempts to transfer this biological knowledge to computer science have led to adequate progress. A good example is one of the deep learning pioneers Terrence Sejnowski, whose achievements can be found in both human brain research and the creation of an artificial brain on this basis^[29-33]. Advances in machine vision were made when the focus was on the characteristics of the objects rather than on individual pixels. Deep learning is therefore effective for solving problems of image analysis because its structure and operation was based on the analysis of the process of vision and image recognition by the human brain. Fortunately, it took much less time than the evolution for creating our species.

What's more, all doctors are already looking forward to the possibility of using navigation, similar to the ones Google has provided in our cars. As we all remember, the development of car navigation was preceded by creating accurate maps. The diagnostics offered by robots are approaching us soon to achieve such accuracy that will enable similar outcomes in medicine. The first is orthopedics and neurosurgery for which we do not require updates in the millisecond time mode. And the first robot tools that used it with great success were the radiosurgical knives of oncological robots (CyberKnife).

AI and robotics are transforming medical services. We note successes in analyzing medical images (histopathology) and building a knowledge base. In 2017, a Chinese robot called Xiao Yi, developed by Tsinghua University passed China's National Medical Licensing Examination. The robot scored 456 points in the test which was well above the passing mark of 360^[34]. OK. So we now have AI with the knowledge of a medical student, but do we have an experienced doctor?

There are several FDA-approved devices and platforms for robotic surgery and these include the da Vinci Surgical System, Sensei X Robotic Catheter System, FreeHand 1.2 and invendoscopy E200 system. Also approved are Flex® Robotic System, Senhance, ARES, the Single-Port Instrument Delivery Extended Research (SPIDER) and the NeoGuide Colonoscope. Other technology platforms waiting for FDA approval include MiroSurge, ViaCath System, SPORT™ Surgical System, SurgiBot, Versius Robotic System, Master and Slave Transluminal Endoscopic Robot, Verb Surgical, Miniature In Vivo Robot, and the Einstein Surgical Robot^[35].

We hope that our robot Robin Heart will soon join this group. Surgical robots are a way to introduce standardization and reduce invasiveness, while ensuring proper operation safety.

"In the future, robotic surgeons will be more involved in the healthcare requirements of individuals. Robots require a communication link and applications that connect the robots to their clients or users. These communication links are usually supported through client/server network connections. Therefore, the networking system is vulnerable to cyber-attacks and consequently, the security and privacy of the robotic platforms is paramount"^[35].

In general, robots will get smarter until they finally become necessary. Despite the problems (temporary, in the category of the time of development of our civilization), artificial intelligence and robots are part of the evolution of humanity and medicine.

DECLARATIONS

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Authors' contributions

The author contributed solely to the article.

Availability of data and materials

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Current management of gastroesophageal reflux disease in the obese population - a review of the literature

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Abstract

The current obesity pandemic has a clear impact on quality of life and health resource utilization; hence it has become a significant global health concern. Multiple obesity-related comorbidities such as gastroesophageal reflux disease (GERD) are frequently observed among this patient population. GERD is a complex disease with multiple elements contributing to the failure of the anti-reflux barrier. If left untreated, the excessive reflux of gastric contents into the esophagus can give rise to multiple complications such as esophagitis, strictures, metaplasia, and cancer. When surgical treatment of GERD is indicated in an obese patient, adequate preoperative evaluation and treatment are critical to achieve durable resolution of symptoms attributed to GERD as well as other obesity related comorbidities. To maximize the potential for a positive outcome, when suitable, gastric bypass surgery rather than sleeve gastrectomy or fundoplication should be strongly considered in the obese patient with GERD.

Keywords: GERD, gastroesophageal reflux disease, bariatric surgery, RYGB, Roux-en-Y gastric bypass, SG, sleeve gastrectomy, fundoplication, BE, Barrett's esophagus

INTRODUCTION

The obesity pandemic has become a significant global health problem. Since 1975, the world prevalence of obesity has nearly tripled, and at least 650 million adults currently have a BMI greater than 30 kg/m².



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The United States is among the countries with the highest rates: more than 30% of adults are currently obese, with rates up to 40% in some regions of the country^[1,2]. Multiple comorbidities have been associated with obesity, and gastro-esophageal reflux disease (GERD) is one of the most common. Interestingly, the incidence of GERD in the United States general population oscillates around 15%, whereas among obese patients it ranges from 22% to 70%^[3,4].

METHODS

A PubMed search was carried out to identify relevant references to include in this literature review. Two senior surgeons, among the authors of this manuscript, reviewed and selected the references among a vast list of available titles.

GERD definition

In 2006, an international group composed of experts in the field of reflux disease achieved consensus on definitions and classifications regarding GERD. Their aim was to establish a universally accepted terminology that could bridge cultures and simplify management, and to initiate collaborative research studies to assist physicians, patients, and regulatory agencies^[5]. GERD was defined as a digestive disorder secondary to persistent gastric contents rising into the esophagus, which can result in a constellation of symptoms and/or complications from chronic acidic exposure. Evidence of troublesome mild symptoms occurring two or more days a week, or moderate/severe symptoms occurring more than once per week were defined as characteristic presentations that could serve for diagnosis.

GERD symptoms can be divided into two categories: typical and atypical. Heartburn, regurgitation, and dysphagia are known as typical symptoms, whereas chest pain, globus sensation, belching, nausea, wheezing, cough, and hoarseness are considered atypical symptoms^[6].

Of note, up to 70% of patients with heartburn symptoms have normal endoscopy. Of those, 50% have abnormal pH tests and thus belong to the non-erosive reflux disease group of patients. The remaining 50% can be divided into functional heartburn and reflux hypersensitivity^[7]. These functional esophageal disorders are characterized by the presence of chronic typical heartburn symptoms attributed to the esophagus without evidence of inflammatory, anatomic, motor, or metabolic disorders as the underlying etiology. Together, these presentations account for 90% of the heartburn patients who fail proton pump inhibitor (PPI) therapy at optimal doses^[8]. It is important to identify this subset of patients, as the usual management of these conditions differs from classic heartburn patients. The current approach to these patients begins with assurance about the nature of their disorder, followed by neuromodulators which are the cornerstone of therapy^[9].

GERD pathophysiology

There are many elements that contribute to the anatomic anti-reflux barriers. The lower esophageal sphincter (LES), the angle of His, the crural diaphragm, phreno-esophageal ligament, and the gastric sling fibers are some of the key components. LES structure and length, anatomic position (including a fundamental intrabdominal portion), innervation, and hormonal control all contribute to its normal function. The LES is not an annular sphincter, but rather formed by two muscle fiber bundles, which have synergistic actions: the “clasp” and the “oblique” muscular fibers. These muscular bundles of approximately 3-cm width cover an area that starts 1.5 cm above the angle of His and ascends to form part of the distal end of the esophagus. These gastric sling fibers form a natural wrap with two arms that extend downwards by running parallel to the lesser curvature^[10,11]. Excitatory and inhibitory neurons affect local sphincter tone by regulating the duration and frequency of transient LES relaxations, thereby facilitating intermittent passage of food into the stomach while preventing reflux back into the esophagus^[12]. The crural diaphragm, which forms the esophageal hiatus and encircles the proximal LES, in addition to the angle of His, helps to

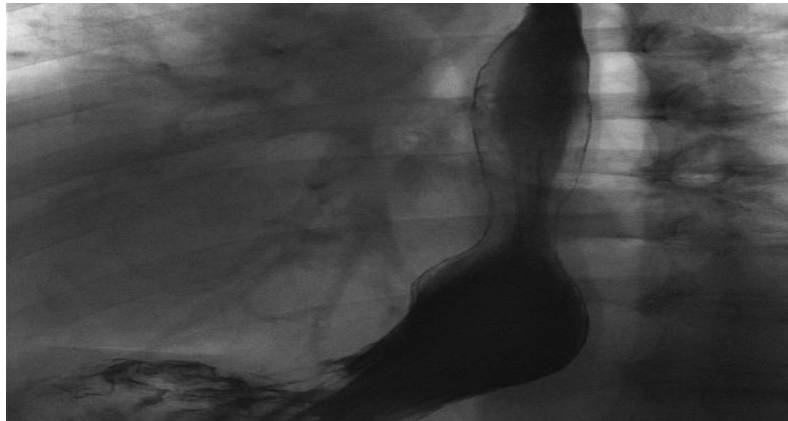


Figure 1. Esophagram showing a hiatal hernia

augment this anatomic region. Moreover, the phreno-esophageal ligament anchors the distal esophagus to the crural diaphragm, preventing excessive sliding during respiratory cycles^[13].

The development of GERD is usually multifactorial. A failure of the anti-reflux barrier that comprises the LES and the crural muscles of the hiatus are common factors in the pathophysiology. Curiously, in a cohort that included 1659 patients with foregut symptoms, Ayazi *et al.*^[14] was able to demonstrate that the presence of a mechanically defective LES, as well as concomitant hiatal hernias [Figure 1], became more prevalent as BMI increased. Indirectly, LES function can be affected by extrinsic variables. Obese patients' susceptibility to develop GERD is intimately related to these indirect variables, which include higher gastric capacity (higher distensibility and disruption of muscle fibers), increased intra-gastric pressure, and augmented positive intra-abdominal pressure as well as negative intra-thoracic pressure^[15-17]. Herbell *et al.*^[18] found that for each five-point increment in an obese patient's BMI, the DeMeester score was expected to increase by three units. Furthermore, from a hormonal standpoint, irregularities in the secretion of adiponectin and leptin from adipose tissue cells has been proposed as a potential nexus between obesity and esophageal metaplasia^[4,19].

GERD complications

GERD complications are related to excessive reflux of acid and pepsin, which can result in necrosis of the mucosa. The amount of injury occasionally outweighs the remodeling capacity of the cellular lining, leading to erosions and ulcers, a condition which is defined as erosive esophagitis. A potential complication seen in GERD patients with esophagitis is the development of peptic strictures. These strictures can occur secondary to persistent injury. Scar tissue forms due to chronic necrosis and inflammation, leading to variable degrees of physiologic contraction of collagen fibers. This phenomenon can cause significant narrowing of the esophageal lumen at the esophago-gastric outlet. This type of benign stricture is usually short segment, circumferential, and amenable to therapeutic dilations for patency restoration. Fortunately, the incidence of strictures has significantly declined since the beginning of the PPI era^[20].

Certain patients can progress to develop metaplastic columnar epithelium which replaces the stratified squamous epithelium that normally lines the distal esophagus [Figure 2]. This is defined as Barrett's esophagus (BE), and the endoscopic prevalence of this phenomenon in the general population is between 0.5% and 2%. For patients with underlying GERD, the prevalence rises to as high as 15%^[21]. In fact, erosive esophagitis is considered an independent risk factor for BE, conferring a fivefold increased risk in a five-year follow-up period^[22]. Not surprisingly, the prevalence of BE in the obese population can be as high as 40%. These alarming rates are some of the reasons why current trends favor aggressive preoperative

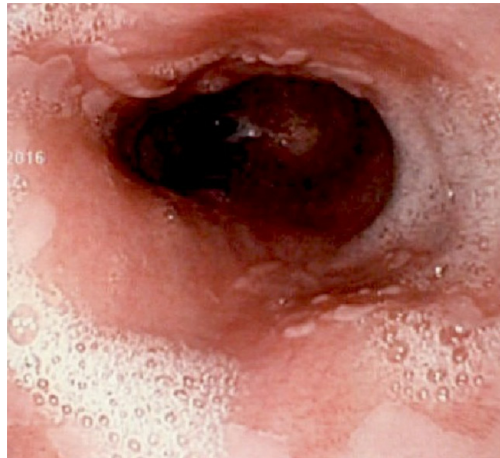


Figure 2. Endoscopy showing changes consistent with Barrett's esophagus

screening in bariatric surgery patients^[23-25]. This patient population is at higher risk of dysplasia and potential development of esophageal adenocarcinoma, as the risk of cancer in BE patients is estimated to be 30-125-fold greater than that of the general population^[26].

To date, neither medical nor surgical treatment seems to guarantee histologic regression of BE. Multiple authors have shown that surgical management results tend to indicate slightly higher resolution and regression rates when compared to medical therapy arms, but these studies lack statistical power, have highly heterogeneous cohorts, and use relatively short surveillance periods^[27-29]. Some authors claim that the main advantage of surgery over medical therapy is that surgery also prevents bile reflux, while proton pump inhibitors control only acid reflux. Other groups have recommended medical treatment because of the less aggressive nature of these therapies when compared to surgery^[30-32]. Regardless, interest in regression of BE with antireflux therapy *vs.* medical therapy has waned in recent years with the rising use of endoscopic ablative techniques such as radiofrequency ablation, which can eradicate the metaplastic mucosa directly^[33].

Regarding the effects of bariatric surgery on BE, a meta-analysis of eight studies that included 117 patients with BE undergoing roux-en-Y gastric bypass (RYGB) found that 56% of these patients had regression of their BE after > 1 year of follow up^[34]. Regression rates of short segment and long segment BE were similar in this study. There have only been a few studies looking at the relationship between BE and laparoscopic sleeve gastrectomy (LSG). Braghetto *et al.*^[35] reported that, in the short term, 1.2% of their post-LSG patients developed BE. However, in this study, patients did not continue endoscopic surveillance past one year if they were asymptomatic. In a study of 110 patients from a single institution in Italy, 17.2% developed a new diagnosis of BE after LSG at a median follow up of 58 months^[36]. The postoperative incidence of GERD symptoms and daily PPI use were also significantly increased. Interestingly, of the patients who had developed BE, 26% had no symptoms of GERD. This finding was also reported in a study by Soricelli *et al.*^[37], in which 21% of post-LSG patients with BE were asymptomatic. Similar rates of “de novo” BE after LSG were reported recently (2019)^[38]. In a multicenter study, 18.8% of patients had developed BE after LSG, with follow up of at least five years. In a study where patients had 10 years of follow up, 15% had developed BE^[39]. Although the malignant transformation potential of BE in post-LSG patients is unknown, the authors of the aforementioned studies have proposed endoscopic screening and surveillance, even in patients without GERD symptoms^[36-39].

DIAGNOSIS

According to current standards of care, for low risk patients with symptoms and history consistent with uncomplicated GERD, empirical therapy with proton pump inhibitors and lifestyle modifications can be

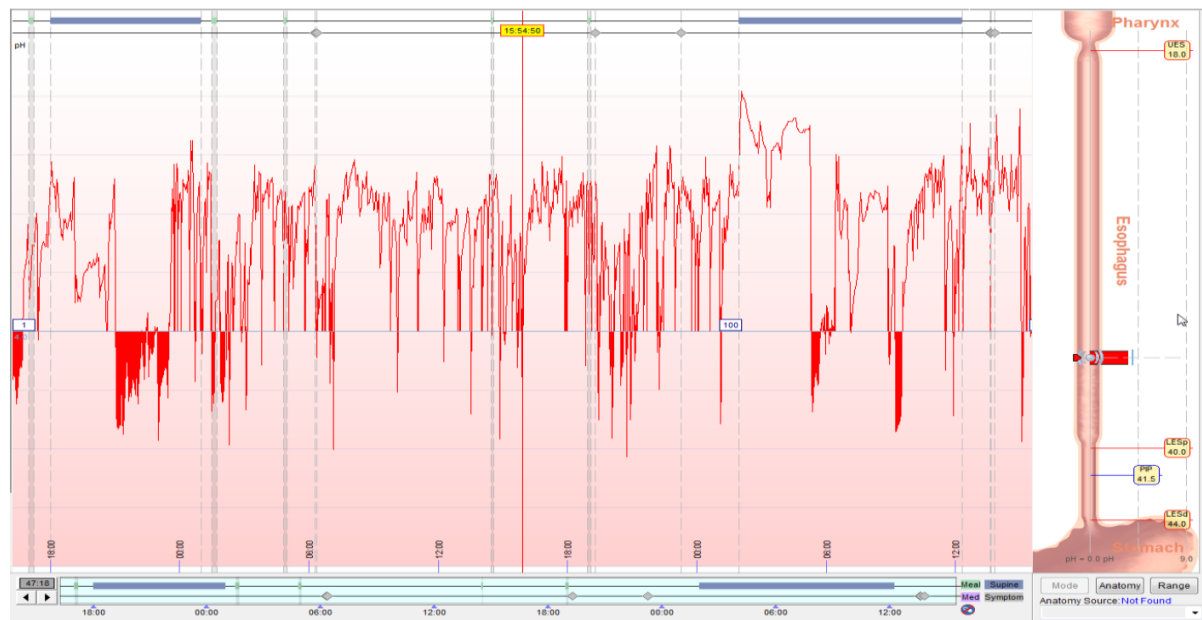


Figure 3. pH Bravo testing showing pathologic reflux

safely offered as an initial approach. On the other hand, for high risk patients with chronic GERD (i.e., Caucasians, males, those greater than 50 years of age, the obese, smokers, and heavy alcohol users), as well as subjects with complications or who fail to respond to conventional medical therapy, further diagnostic testing should be offered^[40].

The classic approach for an objective diagnosis of GERD should involve an esophagram, endoscopy, pH testing, and adjunct motility interrogation via manometry. The barium swallow is a cost-effective, non-invasive technique that offers a global examination of anatomy, swallowing function, motility, and can test for gastro-esophageal reflux. The dynamic images obtained through fluoroscopy serve as a guide for decisions about medical, endoscopic, and surgical management^[41]. Endoscopy can serve as a diagnostic and therapeutic option. This tool facilitates macroscopic evaluation and permits acquisition of specimens for microscopic assessment of esophageal, gastric, and small bowel disease. It can also aid in the management of different pathologies via dilation, plication, ablation, coagulation, *etc.* The gold standard in GERD diagnosis is pH testing. Reflux monitoring allows direct measurement of esophageal acid exposure, frequency, and association with symptoms. A composite pH score or DeMeester score greater than 14.72 indicates pathologic reflux. Reflux monitoring is typically performed using either a wireless capsule or a transnasal catheter (pH alone or combined pH-impedance) with the patient ideally off acid suppression therapy [Figure 3]. Lastly, manometry is most useful for the evaluation of esophageal dysmotility and has only limited utility in the presence of hiatal hernias [Figure 4]. Its role in an anti-reflux surgery work-up is to rule out motility abnormalities that would change the decision making as to which type of operation or wrap should be used for fundoplication. This is perhaps most important in those who present with dysphagia as one of their primary symptoms. The mean delay in diagnosis of achalasia is five years and, as reported by Howard *et al.*^[42], 36.8% of achalasia patients are commonly initially treated for GERD. Even though achalasia and GERD are on opposite ends of the spectrum of LES dysfunction, heartburn and regurgitation are frequently seen in patients who have achalasia^[42-44].

ANTI-REFLUX SURGERY, LSG, AND LAPAROSCOPIC ROUX-EN-Y GASTRIC BYPASS

Surgical therapy for GERD has been shown to be equally effective as medical management, with comparable quality of life scores^[45]. Anti-reflux surgery is considered in patients who have failed

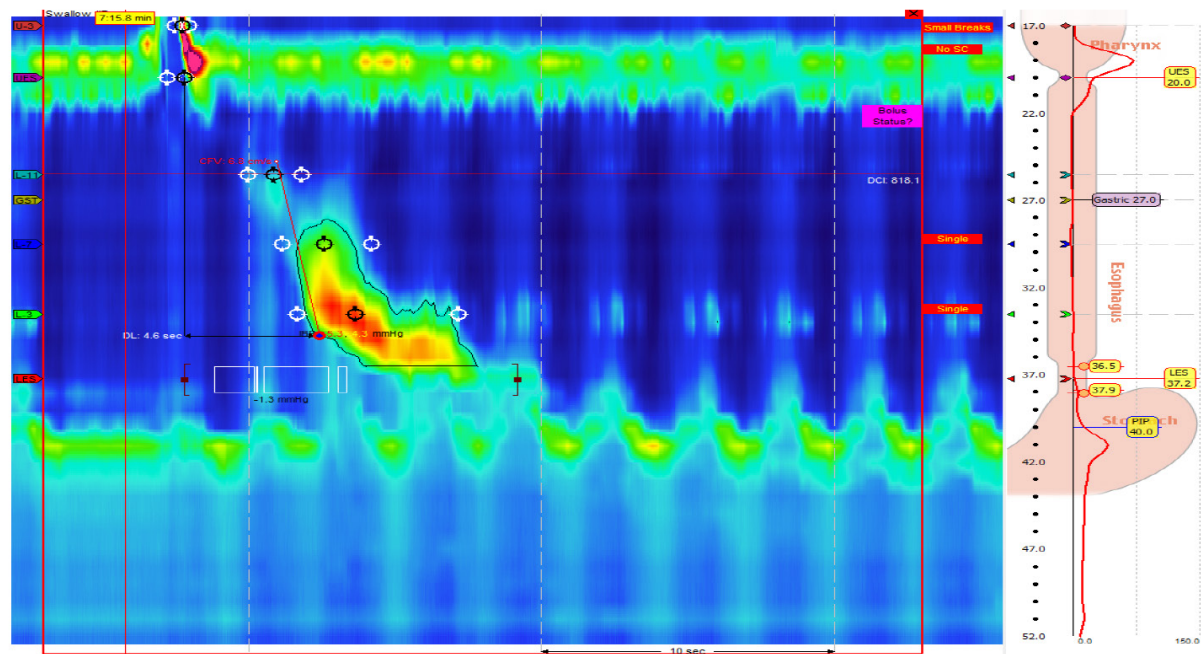


Figure 4. High resolution manometry showing a hiatal hernia and abnormal contraction propagation

medical management, have extra-esophageal manifestations, have complications of GERD, or have a personal preference or medical reason to avoid life-long PPI use. The gold standard laparoscopic Nissen fundoplication and the more recent Linx procedure have been shown to be very successful and equally effective in multiple studies^[46,47]. The literature shows rates of symptomatic recurrence of heartburn less than or equal to 10%, improvement in regurgitation higher than 85%, and long-term satisfaction rates over 90%^[45]. These numbers reflect outcomes in the general population. However, when patients are stratified and segregated by their BMI, results are not as favorable.

The long-term durability of anti-reflux procedures in obese patients is a topic of controversy. The lack of definitive consensus is in part related to the fact that most of the studies available lack statistical power, fail to adequately represent morbidly obese patients, and, most importantly, have limited information on long-term outcomes. The preponderance of the data suggests that durability and efficacy is decreased in obesity [Table 1]. Perez *et al.*^[48] noted an overall symptomatic recurrence rate of 31.3% in obese patients who underwent Nissen or transthoracic Belsey Mark IV fundoplication compared to 4% in normal-weight patients. In a study conducted to determine risk factors for failure of anti-reflux surgery, Morgenthal *et al.*^[49] identified a BMI greater than 35 as a significant risk factor for failure. Interestingly, in an obese cohort undergoing salvage gastric bypass after a failed fundoplication, the incidence of wrap disruption appeared to be higher than the rate of an intact herniated wrap. This observation suggests that the mechanism of failure in obese patients may be different than in the non-obese population^[50].

When compared to Laparoscopic Roux-en-Y Gastric Bypass (LRYGB), the rates of LSG have increased over the last decade. It is now the most commonly performed weight-loss metabolic surgery in the world^[51]. LSG has become popular among surgeons due to its relatively simple technique, lack of anastomoses and fewer potential associated complications. This is problematic, secondary to the significant correlation between obesity and GERD as well as the ill-defined role that the LSG has in the treatment of this cohort. Currently, there is no consensus on the management of GERD in the obese population as it relates to which operation is best, but the data suggest that the RYGB is a superior operation when considering GERD-related outcomes. This is perhaps best illustrated by the fact that postoperative GERD was the most

Table 1. Most relevant manuscripts organized by topic

Author	Year	Journal	Manuscript type	Comments
Kristo et al. ^[6]	2019	<i>Obesity Surg</i>	Retrospective	Testing and GERD in the obese
Patti et al. ^[12]	1997	<i>Surg Clin North Am</i>	Lit Review	GERD
Ayazi et al. ^[14]	2009	<i>Gastrintest Surg</i>	Retrospective	Obesity and GERD
Braghetto et al. ^[3]	2012	<i>Obes Surg</i>	Prospective	RYGB and GERD/Barrett's
Ronkainen et al. ^[22]	2011	<i>Am J Gastroenterol</i>	Prospective	Barrett's endoscopy
Akiyama et al. ^[23]	2009	<i>BMC Gastroenterol</i>	Retrospective	Visceral obesity/Barrett's
Wood et al. ^[24]	2008	<i>Keio J Med</i>	Literature review	Barrett's Esophagus
Corley et al. ^[25]	2007	<i>Gastroenterology</i>	Case control	Obesity and Barrett's
Rossi et al. ^[27]	2006	<i>Ann Surg</i>	Retrospective	Nissen vs. medication Barrett's
Parrilla et al. ^[28]	2003	<i>Ann Surg</i>	RCT	Barrett's, surg vs. medicine
Chang et al. ^[29]	2007	<i>Ann Surg</i>	System Rev	Barrett's medical management
Spechler et al. ^[33]	2014	<i>Dig Dis</i>	Literature review	Barrett's and surgery
Adil et al. ^[34]	2019	<i>Obes Surg</i>	System Rev/Meta-A	RYGB effects on Barrett's
Braghetto et al. ^[35]	2010	<i>Obes Surg</i>	Prospective	Manometry after LSG
Genco et al. ^[36]	2007	<i>Surg Obes Rel Dis</i>	Prospective	GERD/Barrett's - Bariatric Surg
Soricelli et al. ^[37]	2018	<i>Surg Obes Rel Dis</i>	Prospective	GERD/Barrett's - Bariatric Surg
Sebastianelli et al. ^[38]	2019	<i>Obes Surg</i>	Prospective	Endoscopy, Bariatric Surg
Felsenreich et al. ^[39]	2017	<i>Obes Surg</i>	Prospective	GERD/Barrett's Bariatric Surg
Saino et al. ^[46]	2015	<i>J Laparoendosc Adv Surg Tech</i>	Prosp/Multicenter	LINX
Ganz et al. ^[47]	2016	<i>Clin Gastroenterol Hepatol</i>	Retrospective	LINX
Perez et al. ^[48]	2001	<i>Surg Endosc</i>	Retrospective	Obesity and antireflux surg
Morgenthal et al. ^[49]	2007	<i>Surg Endosc</i>	Retrospective	Obesity and antireflux surg
Kellogg et al. ^[50]	2006	<i>Surg Obes Rel Dis</i>	Retrospective	Failed antireflux conv to RYGB
Gagner et al. ^[52]	2013	<i>Obes Surg</i>	Review	LSG consensus
Frezza et al. ^[53]	2002	<i>Surg Endosc</i>	Retrospective	GERD symptoms after RYGB
Schietroma et al. ^[56]	2017	<i>J Obes</i>	Retrospective	GERD/Obesity surgery outcomes
Chiu et al. ^[57]	2011	<i>Surg Obes Relat Dis</i>	Retrospective	Bariatric Surgery and GERD
DuPree et al. ^[58]	2014	<i>JAMA Surg</i>	Retrospective	Bariatric Surgery and GERD
Himpens et al. ^[59]	2010	<i>Ann Surg</i>	Retrospective	LSG outcomes
Oor et al. ^[60]	2016	<i>Am J Surg</i>	System Rev/Meta-A	LSG and GERD
Gu et al. ^[61]	2019	<i>Obes Surg</i>	System Rev/Meta-A	Bariatric Surgery and GERD
Singh et al. ^[63]	2017	<i>Obes Surg</i>	System Rev/Meta-A	Bariatric Surgery, ERAS
Thorell et al. ^[64]	2016	<i>World J Surg</i>	Guidelines	Bariatric Surgery, ERAS

RYGB: roux-en-Y gastric bypass; GERD: gastroesophageal reflux disease; LSG: laparoscopic sleeve gastrectomy; ERAS: enhanced recovery after surgery; LINX: magnetic sphincter augmentation reflux management system

frequently reported complication among surgeons surveyed at the Fourth International Consensus Summit on Sleeve Gastrectomy^[52]. In a review paper drafted by the Society of American Gastrointestinal and Endoscopic Surgeons Foregut Task Force, the LRYGB was identified as the treatment of choice for GERD in obese patients. Authors such as Frezza et al.^[53] showed significant improvement of GERD symptoms after offering LRYGB. His cohort of 152 obese patients with GERD had a substantial decrease in the use of antacid medication by 6 months after surgery. Along these lines, De Groote's systematic review of bariatric surgery and GERD compared various bariatric procedures and found that LRYGB was associated with a notable decrease in GERD. They also analyzed outcomes of the LRYGB compared to lifestyle modifications only, and the former group had better alleviation of GERD symptoms^[54-56].

In contrast to the outcomes seen after LRYGB in GERD patients, there are conflicting data surrounding the relationship between GERD and LSG. In 2011, a systematic review of studies reporting post-LSG GERD rates found no agreement was achieved^[57]. Seven of the studies that were included showed reduced prevalence of GERD after LSG, while four found an increase in GERD. An important limitation of many of these publications is the use of subjective symptoms to confer a diagnosis of GERD rather than objective diagnostic exams. Furthermore, different follow up times and definitions of GERD among these studies made it difficult to make conclusions. In a retrospective review including 4832 bariatric surgery

patients, 70% of patients with preop GERD had no resolution of symptoms after LSG, with 8.6% of patients developing de novo GERD after 3 years^[58]. In another study with six years of follow up after LSG, 23% of patients had GERD compared to 3.6% prior to surgery^[59]. However, in a systematic review that included 33 articles with 8092 post-LSG patients, the authors concluded that there was a trend in increased GERD prevalence following LSG, but no definitive conclusions were attained due to the high heterogeneity of the studies^[60]. In another study which included 3534 obese patients, the occurrence of de novo GERD was 9.3% after LSG and 2.3% after LRYGB. Overall, 40.4% of patients who had undergone LSG eventually showed improvement or remission of GERD, compared to 74.2% of patients in the LRYGB group. The pooled analysis showed that, compared with LSG, LRYGB had a better effect on GERD^[61]. It is impossible to concretely state the risk of GERD following LSG due to the lack of well-designed studies and adequate long-term follow up. Notwithstanding this fact, the data do advocate for the superiority of the RYGB when compared with the LSG in the care of a population with concomitant GERD and obesity.

One of the contributing factors to the difficulty of treating this population is the lack of a consensus on the appropriate preoperative evaluation of the anatomy and function of the foregut prior to a weight loss and metabolic operation. Some authors have advocated for the routine use of EGD and esophagrams, while others have stated that these are not necessary. Many of these papers were published before the LSG era when RYGB and laparoscopic adjustable gastric band were the principal operations offered. With this in mind, Kavanagh *et al.*^[62] protocolized patients with subjective GERD symptoms to undergo preop workup including esophagram and EGD. In the cases where the patient desired LSG, further assessment with esophageal pH testing and high-resolution manometry were ordered. Interestingly, they showed that pathology was commonly found on testing; based on protocol test results, 24.8% of their patients had a change in the procedure selected. Kavanagh *et al.*^[62] set a perfect example of the current trajectory in patient care within the bariatric surgery field. Despite excellent results with the available standardized pathways such as “Enhanced Recovery After Bariatric Surgery”, the field is moving toward offering each patient individualized care based on their comorbidities, functional status, and risk-benefit from surgery^[63-65]. Different calculators can assist surgeons to select the most suitable surgery in order to ensure the best possible outcome. For example, the individualized metabolic surgery score calculator has been proposed for procedure selection based on diabetes severity^[66]. It is used to differentiate patients who have higher odds of improvement/resolution of their diabetes based on disease severity and type of operation. Another example is set by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program risk-benefit calculator^[67]. This tool helps to guide surgical decision-making and informed consent. By implementing 20 patient predictors, this calculator offers information on the likelihood that patients will experience common morbidities and can forecast weight loss and comorbidity resolution. Whether addressing the chance to cure diabetes and GERD or the potential for perioperative morbidity, individualized care based on unique patient characteristics represents the future of surgery in an obese population.

CONCLUSION

Obesity and GERD are both conditions with a significant impact on health-related quality of life and global health resource utilization. The implications of inadequately treated GERD can lead to dangerous complications and need for potentially morbid interventions. There are clear limitations in interpreting the available data due to inconsistency in the definition of GERD. Moreover, the complexity and invasiveness of objective evaluation of GERD can impede its widespread application. However, when surgical treatment of GERD is indicated in an obese patient, adequate preoperative evaluation can maximize the probability of addressing all the patient's comorbidities. In addition, offering LRYGB rather than LSG or fundoplication should be strongly considered in this patient population in order to maximize the potential for a positive outcome.

DECLARATIONS

Authors' contributions

Guided the work, decided on content, concepts discussed, overall edition: Nau PN

Made equal contributions regarding writing, design, edition of the entire manuscript, reviewed corrections and resubmitted the work: Fontan FM, Carroll RS

Made substantial contributions mainly focused on manuscripts selected for references and overall edition: Thompson D, Lehmann RK, Smith JK

Availability of data and materials

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Financial support and sponsorship

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Cause of recurrent laryngeal nerve paralysis following esophageal cancer surgery and preventive surgical technique along the left recurrent laryngeal nerve

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Abstract

Aim: Recurrent laryngeal nerve paralysis (RLNP) after esophageal cancer surgery, especially on the left, is a major clinical challenge. We believe that the use of intra-operative neural monitoring can help us to learn and identify surgical maneuvers that can cause RLNP, so as to improve the postoperative course for patients. Thus, the aim of this study was to determine the causes of RLNP and to devise a preventive surgical technique.

Methods: Radical esophageal cancer surgery was performed with intra-operative neural monitoring at our institution from July 2015 to January 2019. The cause(s) of RLNP was investigated by video analysis, which enabled a preventive technique to be developed and introduced. Short-term surgical outcomes of the modified and conventional surgical methods were compared.

Results: RLNP occurred in 10/57 (17.5%) of cases. The causes of paralysis were traction ($n = 5$), compression ($n = 3$), thermal injury ($n = 1$), and compression in cervical procedure ($n = 1$). Subsequently, 20 surgeries were performed between February and December 2019 using the modified technique and there was only one case (5%) of RLNP.

Conclusion: The main causes of RLNP are compression and traction. Our modified technique for esophageal cancer surgery substantially decreases the incidence of RLNP post-operatively.



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Keywords: Minimally invasive surgery, thoracoscopic esophagectomy, recurrent laryngeal nerve paralysis

INTRODUCTION

Surgery for thoracic esophageal cancer has a high rate of postoperative complications^[1-3] including recurrent laryngeal nerve paralysis (RLNP), which can lead to aspiration pneumonia and voice hoarseness, and greatly affects the postoperative course. Inflammatory complications can also affect the patient's long-term prognosis^[4,5]. Of note, RLNP occurs more frequently on the left, which adds to the clinical challenge.

As such, we introduced intraoperative neural monitoring (IONM) in 2015 and have previously reported on its success in reducing the incidence of RLNP at our hospital^[6]. This can be attributed to three factors: (1) mapping of the recurrent laryngeal nerve (RLN) location; (2) RLN path navigation; and (3) learning effect. Nevertheless, RLNP has not been eliminated completely, largely because the type(s) of surgical maneuver that is responsible is not known.

We hypothesized that with IONM and intra-operative video analysis, the surgical maneuver leading to postoperative RLNP can be identified. Herein, we report our findings from our experiences in applying IONM to esophagectomy. We also describe a modified procedure to prevent RLNP, especially on the left, and the short-term surgical results.

METHODS

Patients

Seventy-seven consecutive patients who underwent prone esophagectomy with radical lymph node dissection at our institution from July 2015 to December 2019 were identified. Of 57 cases treated up to January 2019, 10 (17.5%) developed RLNP and were subjected to detailed video analysis and a preventive surgical technique for RLNP was developed. Since RLNP on the right hardly occurred, we focused on the left. Patients were divided into two groups: conventional surgery (July 2015 to January 2019, $n = 57$) and modified surgery (February 2019 to December 2019, $n = 20$) and short-term surgical outcomes were compared. Cancer staging was performed preoperatively according to the 8th edition of the American Joint Committee on Cancer Staging Manual by endoscopy, enhanced computed tomography, and positron emission tomography^[7]. Postoperative RLNP was evaluated by laryngoscopy on postoperative day 7. We also recorded Clavien-Dindo Grade 2 and higher complications such as aspiration, pneumonia, and anastomotic leakage. In all cases, the first author (Kobayashi H), who had performed more than 100 thoracoscopic esophagectomies prior to this study, performed or supervised the surgery. This study was approved by the institutional review board.

IONM and modified surgical technique

The use of IONM has been described previously^[6]. The modified surgical technique is described in the Result section. Briefly, patients were positioned prone and an electromyographic tracheal tube (Medtronic, Jacksonville, FL, USA), one-lung ventilation with blocker, no muscle relaxation, and NIM Nerve Monitoring System 3.0 (Medtronic) were used. The RLN in the thoracic cavity was localized and confirmed by IONM. At the end of the surgery, the vagal nerve was stimulated with a probe to confirm nerve functioning. Video analyses was performed by the first (Kobayashi H) and second authors (Kondo M) independently. When there was concordance between assessment by the two authors, that particular maneuver would be considered the cause of RLNP.

Statistical analyses

Statistical analyses were performed using JMP version 12.0 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were reported as absolute values and percentages and continuous variables are

Table 1. Patient characteristics and surgical outcomes after technique modification

	Conventional group (<i>n</i> = 57)	Modified group (<i>n</i> = 20)	<i>P</i> value
Gender			1.00
Male:Female	42:15	15:5	
Age			0.71
Median (IQR)	67 (17)	64 (16)	
Body mass index			0.53
Median (IQR)	21.3 (3.5)	21.0 (5.6)	
Smoking yes/no	43/14	12/8	0.19
Alcohol yes/no	50/7	17/3	0.75
Location of the main tumor			0.85
Ce:Ut:Mt:Lt:Ae	1:8:16:31:1	0:3:5:12:0	
Pathological type			0.32
SCC:AC:others	50:5:2	20:0:0	
Prior treatment			0.22
NAC:CRT:ESD:none	26:1:4:26	10:1:1:8	
AJCC Stage			0.23
I:II:III:IV	18:19:19:1	3:6:6:2	
Thoracoscopic:Robotic:Open	44:13:0	0:20:0	< 0.0001
Operative time (min)			0.04
Median (IQR)	295 (71)	266 (62)	
Bleeding (mL)			0.08
Median (IQR)	150 (218)	91 (255)	
Number of dissected mediastinal LNs			0.04
Median (IQR)	24 (13)	29 (12)	
Postoperative left RLNP (laryngoscopy)	10 (17.5%)	1 (5.0%)	0.27
Aspiration (CD2 and over)	2 (3.5%)	1 (5.0%)	1.00
Pneumonia (CD2 and over)	5 (8.8%)	4 (20.0%)	0.14
Anastomotic leakage (CD2 and over)	9 (15.8%)	2 (10.0%)	0.32
Postoperative hospital stay (days)			0.82
Median (IQR)	22 (17)	22 (7)	

IQR: interquartile range; Ce: cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; SCC: squamous cell carcinoma; AC: adenocarcinoma; NAC: neoadjuvant chemotherapy; NACRT: neoadjuvant chemoradiotherapy; ESD: endoscopic submucosal dissection; AJCC: American Joint Committee on Cancer; LNs: lymph nodes; RLNP: recurrent laryngeal nerve paralysis; CD: Clavien-Dindo grade

presented as median and interquartile range. Differences in frequency of categorical variables were assessed with Pearson's chi-squared test or Fisher's exact test, whereas continuous variables were evaluated with the Mann-Whitney two-sample statistic as appropriate. *P*-values < 0.05 were considered statistically significant.

RESULTS

Detection of RLNP

Table 1 shows patients characteristics and short-term surgical results. There were 10 cases (17.5%) of RLNP diagnosed by laryngoscopy on post-operative day 7. The cause of RLNP was determined by video analysis. Typical causes of RLNP identified are shown in Figure 1. Table 2 lists all causes in the 10 cases of RLNP in this study. One of the cases was excluded because the RLNP was thought to be caused by direct nerve compression during cervical procedures. In the other nine, RLNP was found to be caused by traction in the thoracic cavity (*n* = 5), compression (*n* = 3), and thermal injury (*n* = 1).

In terms of the reliability of IONM, the sensitivity (confirmed positive by IONM among verified cases of RLNP) and specificity (negative by IONM among cases of no RLNP) were 80% (8/10) and 95.7% (45/47), respectively [Table 3]. The positive predictive value (percentage of postoperative RLNP cases among RLNP cases estimated by IONM) and negative predictive value (percentage of no postoperative RLNP among patients with no RLNP estimated by IONM) were 80% (8/10) and 95.7% (45/47), respectively.

Surgical technique

Based on the above results, we modified our surgical procedure to try to avoid RLNP. To counter thermal injury, it is necessary to identify the location of the RLN in advance by using IONM as before. We

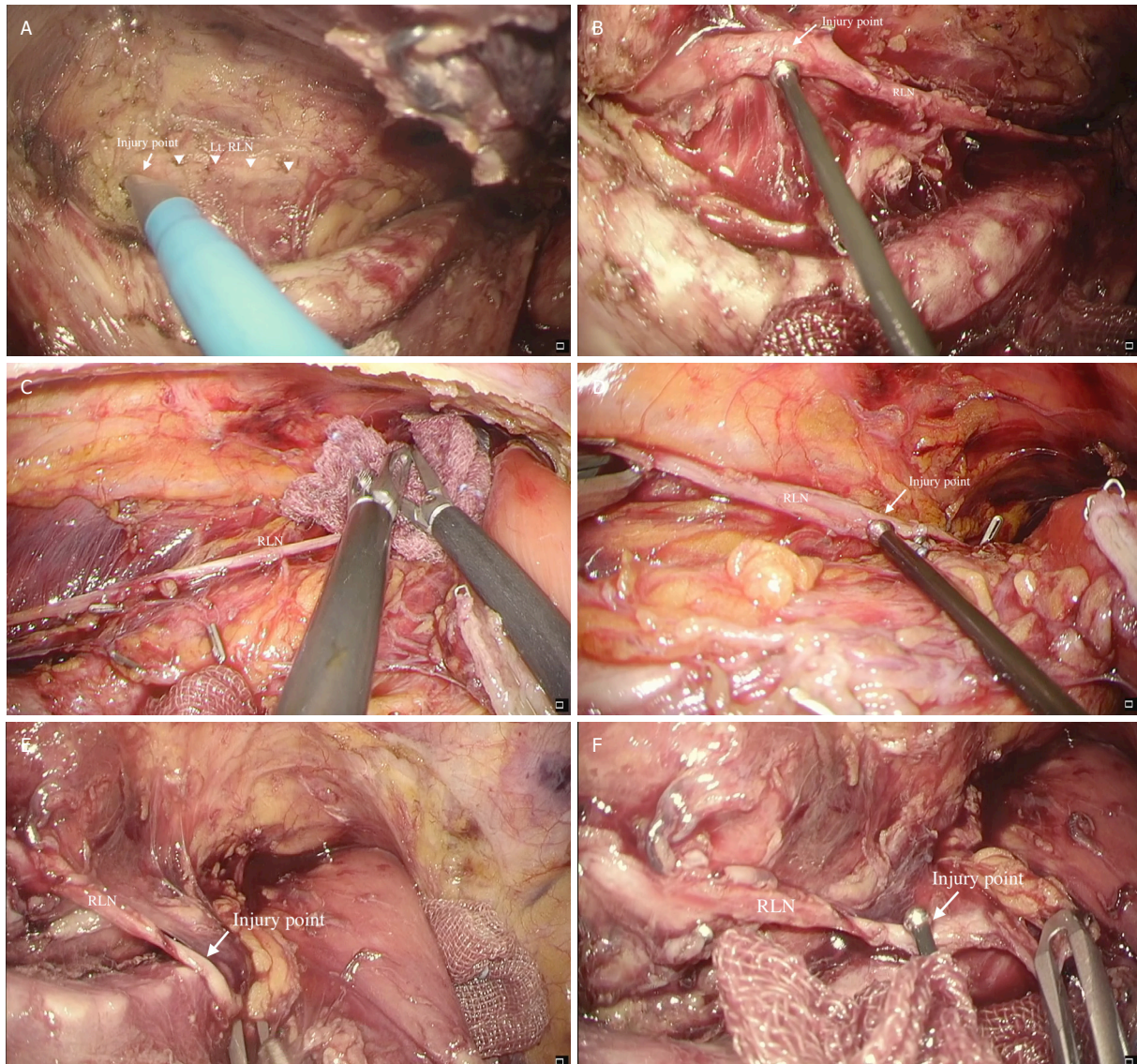


Figure 1. Learning from IONM. The causes of RLNP were revealed by intra-operative video analysis. A, B: in the first case, the electric scalpel touched the RLN before it was recognized (A), resulting in a loss of signal at this point (B). Thermal damage was deemed to be the cause of paralysis in this case. C, D: in the second case, the surgeon compressed the area around the RLN to achieve hemostasis (C). Signal loss occurred at this point (C) and compression of the nerve between the forceps and trachea was determined as the cause of paralysis. E, F: in the third case, excessive traction damaged the RLN at the edge of trachea (E), leading to signal loss. IONM: intraoperative neural monitoring; RLN: recurrent laryngeal nerve; RLNP: recurrent laryngeal nerve paralysis

preferred to use a bipolar device that did not heat up excessively and thus, reduce the spread of heat to the surroundings compared to other energy devices such as laparoscopic coagulating shears. We also avoided traction and compression during the surgery by moving the RLN as little as possible [Figure 2]. The procedure was modified for the left side only; for the right side, we made no changes to the previously reported method^[6]. A supplemental intraoperative video is available.

The esophagus was first severed at the level of the aortic arch, peeled towards the cranial side, and the stump was sewn to the chest wall to expand the operative field [Figure 2A]. We then compressed the trachea to further expand the field of view, and started dissecting lymph nodes around the left RLN [Figure 2B]. Using the glossy membrane as a landmark of the ventral limit of lymph node dissection, we peeled away the adipose tissue, which included the lymph nodes to be dissected [Figure 2C and D]. Next, we removed the

Table 2. Causes of postoperative recurrent laryngeal nerve paralysis

Stretch/Traction	5
Compression	3
Thermal/Heat injury	1
Ligature	0
Transection	0
Others (compression in the neck)	1

Table 3. Results of IONM

	Evaluation with IONM	
	+	-
Motion of vocal cord (POD7)		
+	8	2 Pseudo negative
-	2 Pseudo positive	45

+ means loss of motion of vocal cord checked by ENT doctors or loss of response on IONM; - means no signs of paralysis checked by ENT doctors or adequate response on IONM. IONM: intra-operative neural monitoring; POD: postoperative day; ENT: ear-nose-throat. Sensitivity: 8/10 = 80%; specificity: 45/47 = 95.7%; positive predictive values: 8/10 = 80%; negative predictive values: 45/47 = 95.7%

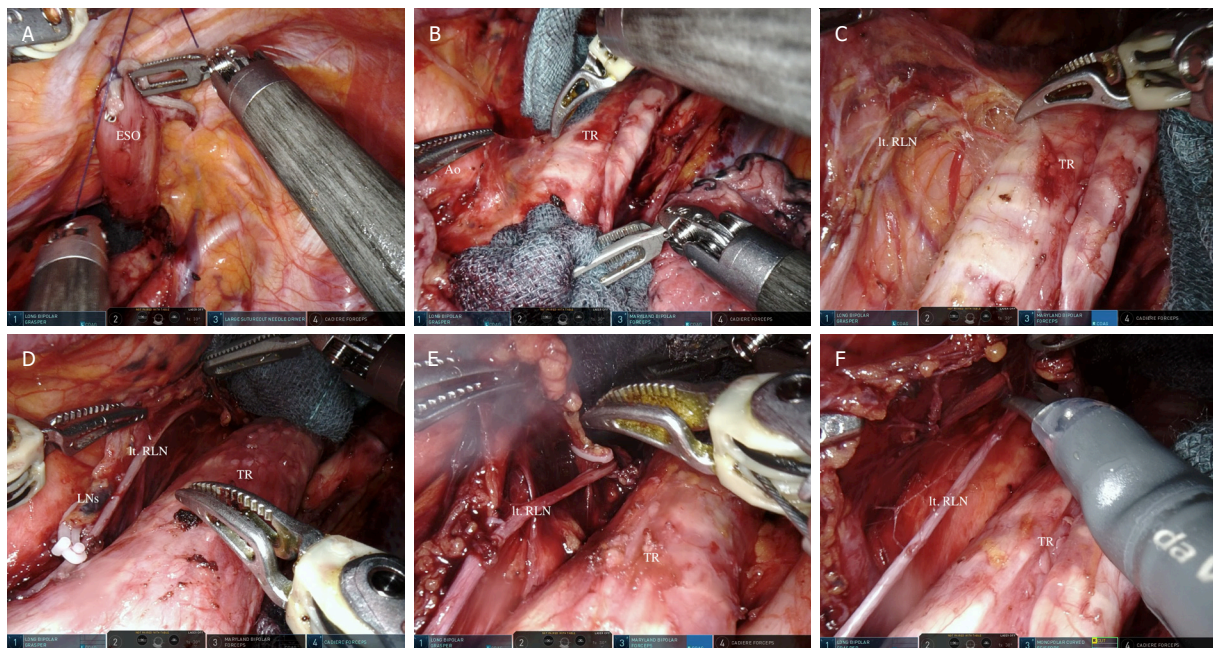


Figure 2. Dissection of lymph nodes around the left RLN. A: the esophagus was cut and the upper side mobilized and sewn to the chest wall; B: by compressing and rolling the trachea, we expanded the operative field of view on the left side and initiated lymph node dissection; C: using the glossy membrane as a landmark on the ventral side, we peeled off the adipose tissue including lymph nodes and proceeded cranially; D: the tissue to be dissected was peeled up behind the RLN; E: hemostasis was achieved by clipping the tracheoesophageal artery; F: connective tissue behind the RLN was cut to complete lymph node dissection around the left RLN. Ao: aorta; ESO: esophagus; TR: trachea; RLN: recurrent laryngeal nerve

tissue towards the dorsal side of the RLN and proceeded towards the cranial side. We clipped the dissected tissue at the most cranial side to achieve hemostasis of the tracheoesophageal artery [Figure 2E]. This clip demarcates the upper end of lymph node dissection from the thoracic cavity and served as a landmark for later dissection of lymph nodes in the neck. We also resected tissue on the dorsal side of the RLN [Figure 2F], which allowed dissection of lymph nodes around the RLN with minimal maneuvering of the nerve, thereby reducing the risk of RLNP. During the cervical procedure, attention to avoid nerve compression by the muscle retractor was necessary.

Short-term surgical results obtained using the modified surgical technique

There were no differences between the conventional and modified surgery groups in terms of sex, age, body mass index, tumor histology and location, clinical stage, preoperative therapy, physical status, and other preoperative risks [Table 1]. None of the cases required conversion to open surgery and there was no intraoperative morbidity in either group. In the modified surgery group, the operation was performed robotically, which significantly shortened the procedure compared to the conventional surgery group (266 min vs. 295 min, $P = 0.04$). There was no significant difference in the estimated total volume of blood loss between groups, although it tended to be lower in the modified surgery group (91 mL vs. 150 mL, $P = 0.08$). The number of dissected mediastinal lymph nodes was significantly higher in the modified surgery group (29 vs. 24, $P = 0.04$). There were also no differences in the rates of complications such as RLNP, aspiration, pneumonia, and anastomotic leakage between the two groups. However, the rate of RLNP tended to be lower in the modified surgery group than in the conventional surgery group (5% vs. 17.5%). The median length of postoperative hospital stay was the same between groups (22 days).

DISCUSSION

RLNP is a relatively frequent complication of esophageal cancer surgery that affects the postoperative course and even overall survival^[1,8]. There are several reports describing the effectiveness of IONM to prevent postoperative RLNP following esophagectomy^[9-11]. At our hospital, the incidence of RLNP has declined since we introduced IONM but it has not been completely eliminated.

The surgical procedure(s) that lead to RLNP remain unclear, and there have not been reports to date addressing this point. In general, the cause was presumed to be either thermal injury from an energy device, or damage through nerve traction or compression. However, without identifying the cause, it is very difficult to implement effective preventive measures. On the other hand, IONM has long been used in the field of Otolaryngology in the treatment of thyroid cancer^[12] and there are many reports on the causes of RLNP after thyroid surgery^[13-15], with traction accounting for 75%-83% of cases. In this study, we found that RLNP following esophageal cancer surgery was similarly, primarily caused by traction and compression, with little contribution from thermal injury. This is the first report describing the causes of RLNP associated with esophageal cancer surgery, albeit in a small number of cases.

We have developed a modified surgical technique to prevent RLNP. Thermal injury occurred relatively early in the surgery and can be prevented by examining the location of the nerve by IONM. In recent years, mesentery-oriented lymph node dissection has become commonplace and has been proposed for esophagectomy^[16]. Accordingly, we dissected the lymph nodes after mesenterization^[6,8]. However, this inevitably increased the risk of strongly pulling the RLN, which could result in RLNP. We therefore concluded that it was difficult to prevent RLNP by this method (conventional surgery group, Figure 3).

The modified surgical technique is suitable for dissecting lymph nodes around the RLN with minimal retraction and compression and has in fact, reduced the rate of RLNP at our institution [Table 1]. Of the 20 surgeries performed after standardizing the procedure, there was only one case of RLNP in which the RLN was seized after misidentification, which counts as a technical error. There have been no instances of RLNP since due to an unidentified cause.

Robot-assisted minimal invasive surgery (Ra-MIE) was used in the modified surgery group for historical reasons. Approved as a medical treatment in Japan since 2018, Ra-MIE is advantageous in esophageal cancer surgery because it allows the operator to manipulate three arms in a stable field of view, even within a narrow space such as the upper mediastinum. Ra-MIE is particularly useful for the delicate manipulation required around the RLN. Thus, Ra-MIE undoubtedly contributed to the impressive results achieved with our modified surgical procedure. However, when comparing 33 Ra-MIE and 44 thoracoscopic surgeries,

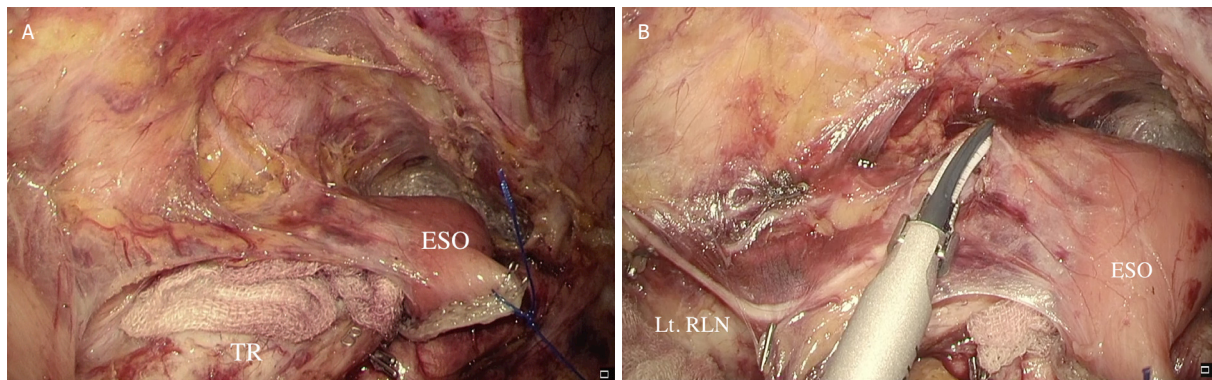


Figure 3. Lymph node dissection around the left RLN with the conventional technique. A: after dissecting the ventral and dorsal sides of the tissues which include the RLN, we divided the esophagus at the level of the aortic arch and drew the upper side of esophagus to the right to expand the operative field; B: the adipose tissue containing lymph nodes was resected while preserving the left RLN. Traction of the esophagus could flex the nerve or cause compression at the corner of the trachea. ESO: esophagus; TR: trachea; RLN: recurrent laryngeal nerve

the RLNP rates were 18% and 11%, respectively (no significant difference). For this reason, we consider the modified surgical procedure to be more important in reducing RLNP.

There were some limitations in this study. First, the study was retrospective, single institution, and included only a small number of cases. Second, we only employed IONM intermittently whereas continuous monitoring may be more useful as it could provide a detailed view of nerve integrity in real time. Finally, our procedure does not allow en-bloc resection of lymph nodes surrounding the RLN, which could be considered as a shortcoming.

In conclusion, we demonstrated that the main causes of RLNP at our institution were due to compression and traction, not thermal injury. We also showed that our modified surgical technique can prevent left RLNP following upper mediastinal lymph node dissection in esophageal cancer surgery.

DECLARATIONS

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Authors' contributions

Designed the study and acquired, analyzed, interpreted of the data: Kobayashi H
Contributed to data interpretation, reviewed the intellectual content of the manuscript, and approved the final version of the manuscript: Kobayashi H, Kondo M, Kita R, Hashida H, Shiokawa K, Iwaki K, Kambe H, Mizuno R, Kawarabayashi T, Sumi T, Kaihara S, Hosotani R

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Case Report

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Use of an intra-aortic balloon pump during laparoscopic sleeve gastrectomy

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Abstract

Heart transplant is the primary treatment for end-stage heart failure; however, morbid obesity limits candidacy. Bariatric surgery performed in patients with advanced heart failure improves eligibility for heart transplantation. This is the first report of an intra-aortic balloon pump used during laparoscopic sleeve gastrectomy. A patient with morbid obesity and non-ischemic cardiomyopathy was referred for weight loss surgery prior to evaluation for heart transplantation. An intra-aortic balloon pump was placed for aggressive diuresis and cardiovascular support during laparoscopic sleeve gastrectomy. The patient did not suffer any complications or require readmission. The use of an intra-aortic balloon pump as a mechanical circulatory system provided a safe laparoscopic sleeve gastrectomy in a patient with advanced heart failure.

Keywords: Heart failure, sleeve gastrectomy, bariatric surgery, cardiac transplant

INTRODUCTION

Heart failure (HF) affects approximately 5.7 million adults in the United States with 5-year mortality approaching 50%^[1]. Heart transplantation is the standard management for advanced HF. However, a body mass index (BMI) ≥ 35 kg/m² is associated with increased early complications, decreased long-term survival, and lower likelihood of receiving an organ^[2,3]. Weight loss results in decreased vascular stiffness and reduction in ventricular hypertrophy^[4]. Bariatric surgery in patients with advanced HF may result in eligibility for heart transplantation. We report the use of an intra-aortic balloon pump (IABP) for perioperative cardiovascular support during laparoscopic sleeve gastrectomy (LSG) in a patient with advanced HF.



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CASE REPORT

A 43-year-old patient with non-ischemic cardiomyopathy, New York Heart Association (NYHA) Class IIIb, and morbid obesity (BMI 45 kg/m²) was referred for weight loss prior to evaluation for heart transplantation. Co-morbid conditions included obstructive sleep apnea, nonalcoholic steatohepatitis, gastroesophageal reflux disease, hyperlipidemia, exertional hypotension, adrenal insufficiency, and 3L continuous oxygen. The patient was diagnosed with HF three years prior with an ejection fraction (EF) of 15%-20%, which required an implantable cardioverter-defibrillator (ICD). Titration of antihypertensive and diuretic medications was limited by syncope and hypotension. The patient was hospitalized over thirteen times with episodes of HF exacerbation and arrhythmias. Ultimately, the ICD was converted to a biventricular device, and EF improved to 25% with complete ventricular pacing. Our patient did not qualify for left ventricular assist devices (LVAD), but still, weight loss surgery was recommended to improve cardiac function and increase the potential for candidacy for heart transplant.

Preoperative care

Our multidisciplinary team consisted of advanced HF and transplant cardiology, cardiothoracic surgery, cardiothoracic anesthesiology, and bariatric surgery. Diet modifications resulted in successful weight loss of 9 pounds over ten months. Preoperative testing included an upper gastrointestinal series that revealed normal esophageal motility, no hiatal hernia, and no gastroesophageal reflux. LSG was chosen over Roux-en-Y gastric bypass for technical ease, shorter operative time, perioperative safety profile, and effective weight loss in end-stage HF patients^[5-7].

To address the perioperative risks of volume shifts and hemodynamic instability, preoperative placement of an IABP was considered. The IABP was necessary to establish euvolemia prior to surgery and maintain adequate cardiac output during laparoscopy. Over six months, the patient obtained clearances from nutrition, psychology, endocrinology, pulmonology, and cardiology. The patient was pre-admitted to the advanced HF team to address fluid shifts prior to surgery. An IABP was placed on hospital day 2 to prevent hypotension with ongoing, supervised diuresis. A catheter was inserted through the right femoral artery with a 7.5F sheath and advanced under fluoroscopic guidance into the descending thoracic aorta. The IABP was turned on with continuous heparin infusion until 6 hours prior to surgery. Successful diuresis was achieved with a negative fluid balance of 5 liters, without episodes of hypotension.

Surgical technique

Upon arrival to the operating room, the IABP was transferred from battery to an alternating current power. After additional arterial and venous access was achieved, the case began with the placement of four ports in the subcostal area with the option of low-pressure insufflation. The patient was gradually positioned in reverse Trendelenburg as hemodynamic status was monitored. A liver retractor was placed to expose the gastroesophageal junction. The greater curvature of the stomach was mobilized to the left crus with cauterization of the short gastric blood vessels. Hemostasis was achieved and a 36F bougie was passed into the gastric lumen. Sleeve gastrectomy was performed using staplers, at 4-5 mm and 3-4 mm staple heights, with staple line reinforcement. Care was taken to ensure the incisura was not narrowed. An esophagogastroduodenoscopy was performed with a negative leak test and symmetric stomach. Blood loss was less than 50 mL and hemodynamic stability persisted throughout the case. The patient tolerated the procedure without any complications and the continuous heparin infusion was restarted.

Post-operative outcomes

Diet was advanced on post-operative day (POD) 1 and the IABP was removed on POD 2. The patient was discharged on POD 9 without complications, blood transfusions, or readmission. Follow-up visits with the bariatric surgeon, dietitian, psychologist, or advanced HF cardiologist occurred at 3 weeks, 3 months, 6 months, and 1 year. Progressive weight loss occurred at 3 weeks with 8 percent excess weight loss (%)

EWL), 3 months with 21% EWL, and 6 months with 27% EWL. At 12 months, the patient had 39% EWL, reached a BMI of 36 kg/m², and was 11 pounds from the goal weight. Exercise tolerance improved, oxygen was no longer required, and NYHA Class II-III symptoms were noted. In addition, hospitalizations for HF decreased to two admissions over one year and EF was stable at 25%. By 15 months, the patient presented in cardiogenic shock and ultimately required LVAD placement for cardiac stabilization.

DISCUSSION

Obesity is a risk factor for the development of cardiovascular disease and HF. Heart transplant is the primary treatment for end-stage HF; however, morbid obesity is a relative contraindication to transplantation^[8]. A BMI ≥ 35 kg/m² is associated with early complications and decreased long-term survival after heart transplant, compared to class I obesity^[2]. Weight loss improves cardiovascular function through increased left ventricular diastolic and systolic function, reduction of myocardial oxygen consumption, and reversal of impaired aortic distensibility^[4]. The Swedish Obese Subjects study demonstrated sustained weight loss and decreased cardiovascular events, including death, after bariatric surgery^[9]. Thus, bariatric surgery is an effective intervention for morbidly obese patients who require weight reduction to become a candidate for heart transplantation.

Bariatric surgery in patients with severe cardiomyopathy, including LVAD, is an opportunity for rapid weight loss as a “bridge” to transplantation. Studies of small cohorts show patients with LVAD who underwent bariatric surgery had improvement in median left ventricular ejection fraction and reduction in NYHA classification^[6,10]. In particular, Punchai *et al.*^[6] reported on three patients with LVAD who went on to receive a heart transplant after LSG. Acceptable rates of complications included five perioperative morbidities and two deaths from LVAD complications. LVAD complications occur at a rate of 8%-29% and include: bleeding, infection, neurologic event, and anticoagulation issues^[11]. In addition, mechanical circulatory support devices are associated with heightened healthcare costs. The total cost for LVAD as a bridge to transplantation ranges from \$316,078 to \$1,025,500^[12]. Further cost of management includes the median cost of a single readmission at \$7,546; with up to 81.8% of LVAD patients requiring readmission^[12]. Options for our patient were to perform weight loss surgery: (1) after further deterioration that required LVAD implementation or (2) with the option of temporary mechanical support with IABP. The early intervention of LSG improved cardiac function and symptoms for more than one year although, an episode of cardiogenic shock ultimately required LVAD placement. While the progression to LVAD is an acceptable risk, this case describes the multidisciplinary team approach critical to successful LSG in a patient with complex heart disease.

To the best of our knowledge, this is the first report of the temporary use of an IABP to achieve uncomplicated bariatric surgery in a high-risk patient with advanced cardiac disease. The IABP has been utilized to establish hemodynamic stability in patients awaiting cardiac surgery with decompensated HF^[13], but rarely reported in non-cardiac surgery. Successful placement of an IABP in patients with congestive HF who underwent non-cardiac procedures (nephrectomy, colectomy with splenectomy, and an exploratory laparotomy) potentially reduced morbidity and mortality^[14]. Similarly, the temporary mechanical circulatory assistance of the IABP resulted in a successful LSG, without morbidity or mortality. As a result, the multidisciplinary team approach resulted in safe bariatric surgery, in a hospital with the infrastructure to manage advanced HF.

In conclusion, the temporary application of an IABP provides cardiovascular support to achieve a safe LSG. A multidisciplinary team approach is recommended for perioperative management of advanced HF.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception, writing, and literature review of the case report: Narvaez A, Perez JE, Castro M, Seymour KA

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Technical Note

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Mediastinoscopic esophagectomy with lymph node dissection using a bilateral transcervical and transhiatal pneumomediastinal approach

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Abstract

We developed a method for mediastinoscopic esophagectomy via a bilateral transcervical and transhiatal approach under pneumomediastinum as a less-invasive radical operation. The right recurrent nerve is first identified using an open approach, and the right cervical paraesophageal lymph nodes and part of the right recurrent nerve lymph nodes are dissected, after which pneumomediastinum is initiated. The upper thoracic paraesophageal lymph nodes and right recurrent nerve lymph nodes are dissected along the right vagus nerve. The dorsal side of the esophagus is dissected along the visceral sheath taking care to avoid thoracic duct injury and is then dissected along the vascular sheath in front of the descending aorta. The esophagus is dissected from the trachea at the caudal side of the aortic arch, and then dissected along the ventral side of the left main bronchus, reaching the pulmonary artery. Finally, the right recurrent nerve lymph nodes around the right subclavian artery are completely retrieved. The left cervical approach is almost the same as that via the right side. The dorsal side of the esophagus is almost dissected along the visceral sheath with a right transcervical approach. The subaortic arch to the left tracheobronchial lymph nodes are dissected using the crossover technique. These lymph nodes are easily dissected by cutting the left and ventral side of the lymph nodes because the caudal side is already dissected in the right transcervical approach. A bilateral (especially right trans-cervico-pneumomediastinal) approach is useful for bilateral upper mediastinal lymph node dissection and esophagectomy.

Keywords: Minimally invasive esophagectomy, cervical approach, esophageal cancer, mediastinoscopic esophagectomy, pneumomediastinum, mediastinoscopic esophagectomy with lymph node dissection



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INTRODUCTION

Conventional radical esophagectomy through right thoracotomy is one of the most invasive procedures. It is important to reduce the invasiveness of this procedure.

Conventional radical esophagectomy was previously performed for the treatment of mucosal esophageal cancers for patients diagnosed with not only advanced esophageal cancer but also T1a N0 M0 cStage I according to the Union for International Cancer Control TNM Classification (eighth edition)^[1]; however, endoscopic submucosal dissection has come to be performed for patients with T1a N0 M0 cStage I as minimally invasive treatment and the methods have been well established^[2].

On the other hand, the esophagectomy with dissection of the mediastinal and abdominal lymph nodes is needed for the treatment of thoracic esophageal cancer with invasion of the submucosal layer or deeper layers. For the abovementioned reason, hybrid surgery consisting of a two-field abdominal-thoracic operation (called the Ivor-Lewis procedure) was developed^[3]. In Western countries, abdominal esophageal cancer and esophagogastric junctional cancers are well observed and later histological types are frequently diagnosed as “adenocarcinoma”. Thus, this procedure is considered reasonable because esophageal cancers at these locations are rarely associated with upper mediastinal and cervical lymph node metastasis. Esophageal cancers in the thoracic esophagus are frequently associated with upper mediastinal and cervical lymph node metastasis. Thus, this procedure is not suitable for these esophageal cancers. To resolve this problem, McKeown developed total esophagectomy with three-field lymph node dissection^[4].

Currently, radical esophagectomy through right thoracotomy has changed to esophagectomy via a thoracoscopic or laparoscopic approach, including robot assisted surgery, which reduces the invasiveness of the procedure by decreasing the destruction of thoracic and abdominal walls^[5-11]. However, this method mandates the use of one-lung ventilation, some destruction of the thoracic wall, or prone positioning.

Conventional transhiatal esophagectomy has been performed and mediastinoscopic esophagectomy has been developed. These procedures are also recognized as types of minimally invasive esophagectomy (MIE)^[12-14]. However, due to the blind maneuvering in the upper and middle mediastinum that is necessary in this procedure and the difficulty of systematic lymph node dissection, it is usually only applied in limited cases, such as cases of esophagogastric junction cancer, very early-stage cancers, or some cases of advanced thoracic esophageal cancer for the purpose of palliative resection^[12].

Recently, we developed and reported the performance of “mediastinoscopic esophagectomy with lymph node dissection (MELD)” under pneumomediastinum using a bilateral transcervical and transhiatal approach, as a method of radical esophagectomy^[15-18]. This procedure achieves curative radical esophagectomy with minimal invasiveness. Upper mediastinal lymph node dissection has been performed using bilateral open cervical surgery and a left transcervical and transhiatal pneumomediastinal approach in some institutions^[19,20]. However, in the results of our clinical trial, the right recurrent nerve lymph nodes, the upper thoracic paraesophageal lymph nodes, and the subaortic arch to the left tracheobronchial lymph nodes could not be completely dissected using the left transcervical approach alone^[17,18]. We are therefore of the opinion that a right cervical pneumomediastinal approach is necessary to achieve the complete dissection of these lymph nodes. We herein describe the surgical technique using a bilateral (especially right cervico-pneumomediastinal) approach.

TECHNIQUE

In the MELD procedure, the right cervical approach is performed first, followed by the left cervical approach and laparoscopic-transhiatal approach.

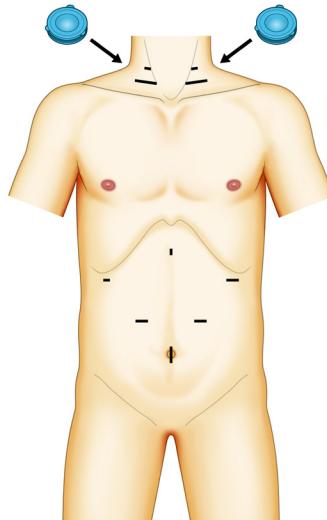


Figure 1. The location of the ports and single-port laparoscopic access devices. This schematic illustration shows single-port laparoscopic access devices in the bilateral cervical area and ports in the abdominal area. A single-port laparoscopic access device with three 5-mm trocars is placed in a triangle configuration. Approximately 3 cm above this device, a 5-mm trocar is inserted as a mediastinoscopic port

Right cervical approach

A right cervical collar incision (approximately 6 cm) is made 3 cm above the right clavicle, and sufficient working space is created between the tracheoesophageal groove and right carotid sheath. The right recurrent nerve is first identified using an open approach and part of the right cervical paraesophageal lymph nodes and the right recurrent nerve lymph nodes between the tracheal wall and the right recurrent nerve are dissected.

After a single-port laparoscopic access device (Lap Protector; Hakko Corporation, Nagano, Japan) is inserted in the wound to exclude the right lobe of the thyroid gland, the cervical wound is sutured over a length of approximately 4 cm. The device is placed at the dorsal side of the sternohyoid and the scapulothyoid muscles at the cranial side, at the inner border of the sternal head of the sternocleidomastoid muscle on the outside, and at the dorsal side of the clavicular head of the sternocleidomastoid muscle on the caudal side. Next, an EZ access (Hakko Corporation, Nagano, Japan), through which three 5-mm trocars are placed in a triangle configuration [Figure 1], is attached. Then, pneumomediastinum (to 8 mmHg) is established with CO₂. A 5-mm trocar is inserted as a mediastinoscopic port approximately 3 cm above this device; we can observe the whole forceps movement from the beginning of forceps insertion. A laparoscopic forceps and a LigaSureTM Maryland (Medtronic, Minneapolis, MN) are inserted between the tracheal wall and the internal side of the right recurrent nerve [Figure 2A and B]. The upper thoracic paraesophageal lymph nodes and the right recurrent nerve lymph nodes are dissected along the right vagus nerve with attention paid to avoid injury of the right mediastinal pleura [Figure 3]; then, the proximal portion of the azygos vein and the right bronchial artery are dissected [Figure 4A and B]. Next, the dorsal side of the esophagus is dissected along the visceral sheath with attention paid to avoid the injury of the thoracic duct, which is located on the dorsal side of the visceral sheath [Figure 5]. The esophagus is dissected along the vascular sheath in front of the descending aorta, because the visceral sheath becomes unclear on the caudal side of the bifurcation of the trachea [Figure 4 A and B]. During dissection, the proper esophageal artery is double sealed and cut using a LigaSureTM Maryland. Then, the esophagus is dissected from the trachea on the caudal side of the aortic arch. In some cases, the broncho-oesophagus muscle is developed and attention should be paid to avoid injury of the membranous portion of the trachea. Next, dissection is performed along the ventral side of the left main bronchus, reaching to the pulmonary artery, in order to determine the caudal side of the lymph nodes in the subaortic arch to the

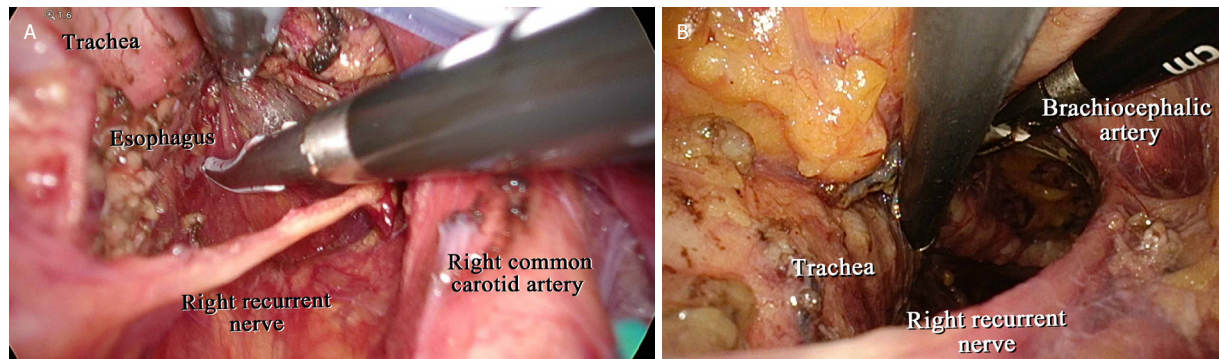


Figure 2. A,B: dissection via a right transcervical approach under pneumomediastinum. The laparoscopic forceps and a vessel sealing system are inserted between the tracheal wall and the internal side of the right recurrent nerve

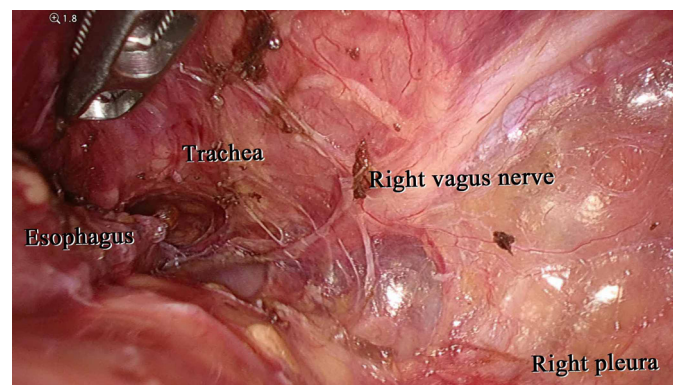


Figure 3. Dissection of the right side of the esophagus via a right transcervical approach under pneumomediastinum. The upper thoracic paraesophageal lymph nodes and right recurrent nerve lymph nodes are dissected along the right vagus nerve with attention paid to avoid injury to the right mediastinal pleura

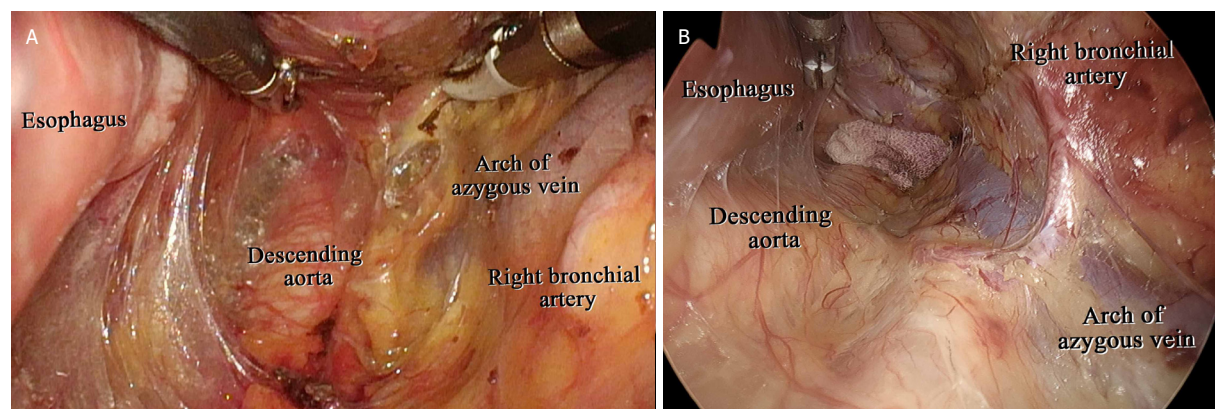


Figure 4. A, B: dissection of the right dorsal side of the esophagus via a right transcervical approach under pneumomediastinum. The proximal portion of the azygos vein and the right bronchial artery is observed along the right mediastinal pleura. The esophagus is dissected along the vascular sheath in front of the descending aorta, because the visceral sheath becomes unclear on the caudal side of the bifurcation of the trachea

left tracheobronchial region, which should be dissected. To make it easy to dissect the left recurrent nerve lymph nodes, the left recurrent nerve is exposed in the right transcervical pneumomediastinal approach [Figure 6].

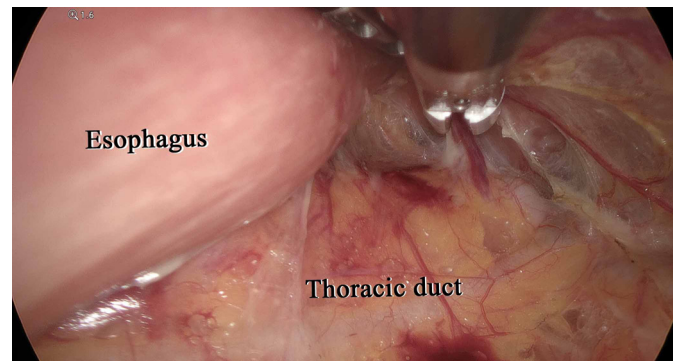


Figure 5. Dissection of the dorsal side of the esophagus via a right transcervical approach under pneumomediastinum. The dorsal side of the esophagus is dissected along the visceral sheath with attention paid to avoid injury to the thoracic duct, which is located on the dorsal side of the visceral sheath

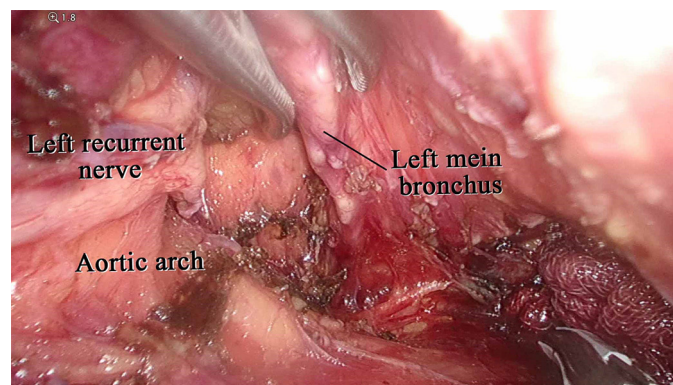


Figure 6. Dissection of the cartilage of the left main bronchus via a right transcervical approach under pneumomediastinum. Dissection of the subaortic arch to the left tracheobronchial lymph nodes is performed along the ventral side of the left main bronchus reaching to the pulmonary artery to determine the caudal side of the lymph nodes in the subaortic arch to the left tracheobronchial region, which should be dissected. To enable the easy dissection of the left recurrent nerve lymph nodes, the left recurrent nerve is exposed via the right transcervical pneumomediastinal approach

Finally, after the common carotid artery is pulled outward and the esophagus is pulled to the left side, the right recurrent nerve lymph nodes around the right subclavian artery are completely retrieved [Figure 7]. Under pneumomediastinum, these lymph nodes can be completely dissected.

Left cervical approach

A left cervical collar incision and scope port site are made symmetrically. After identifying the cranial portion of the left recurrent nerve, which is located on the dorsal side of the inferior part in the left lobe of thyroid gland, some of the left cervical paraesophageal lymph nodes and left recurrent nerve lymph nodes are dissected by the open method.

After a single-port laparoscopic access device is inserted into the wound, the cervical wound is sutured over a length of approximately 4 cm.

The device is placed at the dorsal side of the sternohyoid and the scapulohyoid muscles on the cranial side, at the inner border of the sternal head of the sternocleidomastoid muscle on the outside and at the dorsal side of the clavicular head of the sternocleidomastoid muscle on the caudal side. After attaching an EZ access and inserting a 5-mm trocar as a mediastinoscopic port, left transcervical pneumomediastinum is applied similarly to the right side. First, the dissected layer on the dorsal side of the esophagus and from the

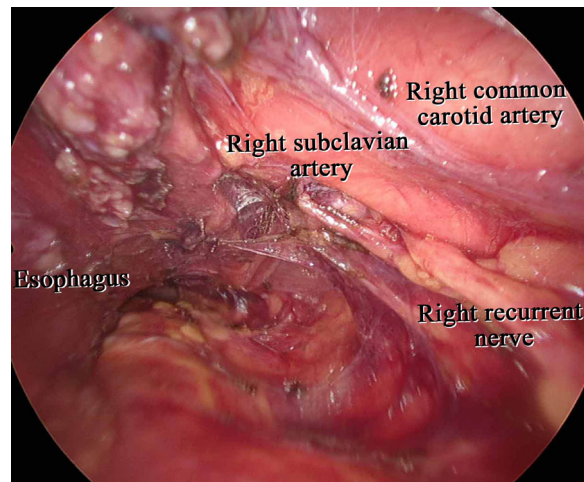


Figure 7. Dissection of the right recurrent nerve lymph nodes via a right transcervical approach under pneumomediastinum. After the right common carotid artery is pulled outward and the esophagus is pulled to the left, the right recurrent nerve lymph nodes around the right subclavian artery are completely retrieved

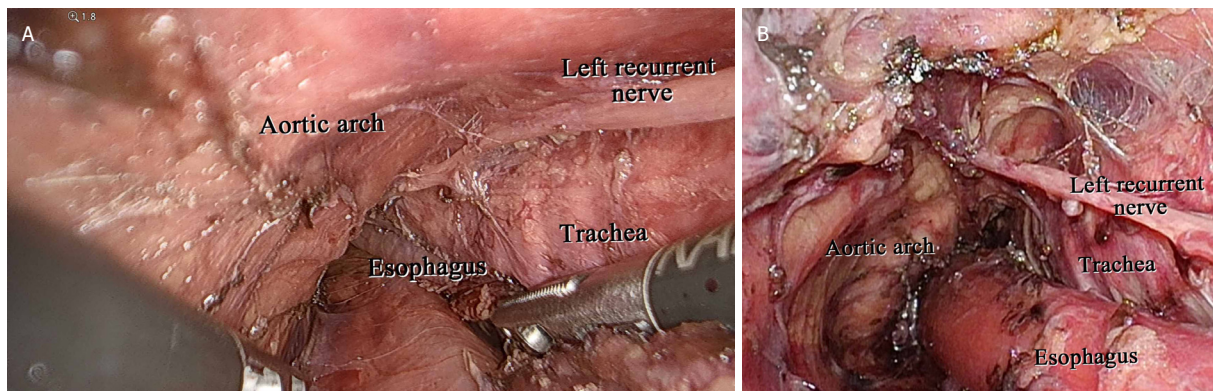


Figure 8. Dissection of the left recurrent nerve lymph nodes via a left transcervical approach under pneumomediastinum. A: the left recurrent nerve lymph nodes are dissected along the dorsal side of the left recurrent nerve; B: the ventral side of the left recurrent nerve lymph nodes are dissected along the left recurrent nerve and the tracheal branch of the left recurrent nerve is preserved as much as possible

right side is checked and dissection is performed to near the aortic arch with attention paid to avoid injury to the visceral layer. In many cases, the esophagus has already been mostly dissected by the right transcervical approach. Next, the esophagus is dissected from the left subclavian artery, reaching to the aortic arch.

The ventral side of the esophagus is dissected from the left side of the membranous portion of the trachea, the left main bronchus, and the aortic arch. The left recurrent nerve lymph nodes are dissected along the dorsal side of the left recurrent nerve [Figure 8A]. Because of this procedure, the left recurrent nerve and the ventral side of the left recurrent nerve lymph nodes are attached to the left side of the trachea. Because the left recurrent nerve at the recurrent portion on the aortic arch has already been exposed via the right transcervical approach, the recurrent nerve is easily detected. We think that this method is useful for preventing left recurrent nerve injury.

Next, the ventral side of the left recurrent nerve lymph nodes is dissected along the left recurrent nerve [Figure 8B], and the tracheal branch of the left recurrent nerve is preserved as much as possible^[21]. We consider that this method is useful for two reasons: First, appropriate tension can be placed on the left

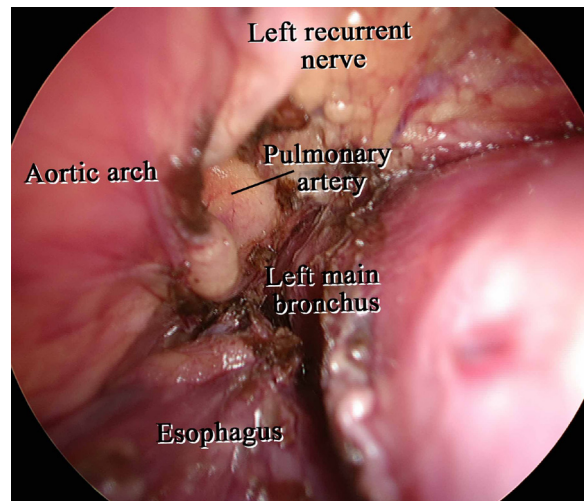


Figure 9. Dissection of the subaortic arch to the left tracheobronchial lymph nodes via a left transcervical approach under pneumomediastinum. These lymph nodes can easily be dissected by cutting only the left and ventral side of these lymph nodes while pulling the esophagus toward the right side because the caudal and dorsal side of these lymph nodes have been already dissected via a right transcervical approach

recurrent nerve lymph nodes and the dissection of these lymph nodes can be easily performed because the left recurrent nerve is attached to the tracheal wall. Second, the branch of the left recurrent nerve is considered useful for preserving the cough reflex.

Dissection of the subaortic arch to the left tracheobronchial lymph nodes

The subaortic arch to the left tracheobronchial lymph nodes is dissected using the crossover technique, as described previously^[15-18]. The crossover technique consists of the transhiatal, right transcervical, and/or left transcervical approach and is suitable for dissection in narrow and relatively deep operative fields, as the approach can be made from two directions. We use this technique when dissecting the subaortic arch to the left tracheobronchial lymph nodes. First, the caudal and dorsal sides of these lymph nodes are dissected via the right transcervical approach. The lymph nodes can then be dissected by cutting only their left and ventral sides with the esophagus pulled toward the right via the left transcervical approach [Figure 9].

Laparoscopic and transhiatal approach

The ports are located in an inverted trapezoidal shape, as described in Figure 1, in accordance with laparoscopic gastrectomy. Pneumoperitoneum with CO₂ (to 10 mmHg) is then introduced. After the dissection of the upper abdominal lymph nodes and gastric conduit mobilization, the esophagus is cut at cranial side as much as possible. The suture thread at the cut end of the esophagus is pulled to provide traction for the dissection of the middle to lower mediastinal lymph nodes, including the subcarinal lymph nodes under pneumomediastinum [Figure 10]. In our institute, this is performed using totally endoscopic surgery. We often use the ENSEAL® G2 Articulating Tissue Sealer (Ethicon Endo-surgery, Cincinnati, Ohio), which is a curved long bipolar sealer, because the subcarinal nodes are difficult to dissect from abdominal ports.

Range of the operation field in the cervical and transhiatal approach under pneumomediastinum

The dorsal side of the esophagus from the cervical area to near the pulmonary vein is easily dissected via the cervical pneumomediastinal approach. On the other hand, the subcarinal lymph nodes are easily dissected via a transhiatal pneumomediastinal approach rather than a cervical approach. This is for the following reasons. First, these lymph nodes can be easily dissected *en bloc* with the esophagus via transhiatal approach but not via a cervical approach. Second, bleeding from the subcarinal lymph nodes connected to the pretracheal lymph nodes cannot be stopped easily via a cervical approach.

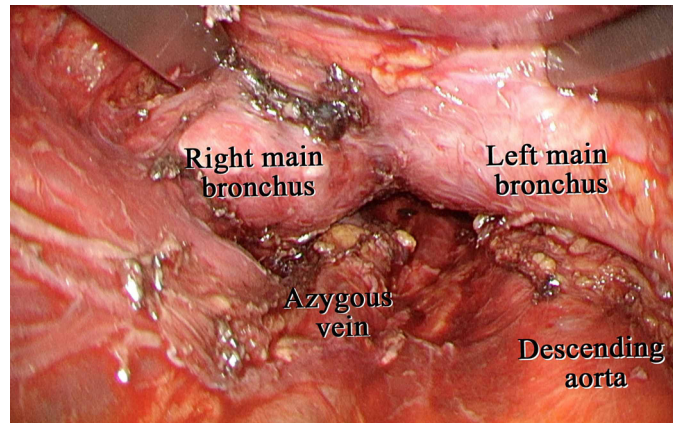


Figure 10. Subcarinal lymph node dissection via a transhiatal approach under pneumomediastinum. The middle to lower mediastinal lymph nodes, including the subcarinal lymph nodes, are dissected under pneumomediastinum via a transhiatal approach

We consider the “crossover technique” to be useful for the dissection of the lymph nodes near the bilateral main bronchus because these lymph nodes are located in the deepest area via both the cervical and transhiatal approaches.

After the pneumomediastinal procedure, the bilateral remnant cervical paraesophageal lymph nodes and supraclavicular lymph nodes are dissected using an open method.

The median total number of dissected lymph nodes in the cervico-mediastinal region identified with a mediastinoscope was 36 (range 22-76) in 10 cases treated using the MELD procedure in our institute.

Postoperative outcomes

This operation using the bilateral cervical approach under pneumomediastinum was performed for 10 cases. The median mediastinoscopic operation time was 312 (299-336) mins and the median blood loss was 476 (203-667) mL. The median postoperative stay was 15.5 (14.0-16.8) days.

DISCUSSION

The MELD procedure is considered to have several advantages over other approaches. First, this procedure does not require one-lung ventilation or a prone position. Second, this procedure requires only bi-cervical and abdominal ports, thus no thoracic wounds are made, and the surgical wounds are very small. Finally, the view via the right transcervical approach under pneumomediastinum is similar to that via the right transthoracic approach.

Concerning the surgical outcomes, the blood loss was slight, and the postoperative stay was short. In addition, dissection of the mediastinal lymph nodes using our MELD procedure was not inferior to that with thoracoscopic esophagectomy^[22]. These results and the known benefits thus indicate that this procedure is promising and expected to become prevalent in the near future.

However, this procedure is considered to have some disadvantages as well. This procedure requires a long operation time, and recurrent nerve palsy is more frequently observed than with thoracoscopic esophagectomy^[10]. In our institute, recurrent nerve palsy was recognized in about 40% of cases treated with this procedure. However, most cases recovered within six months. We speculate that recurrent nerve palsy occurred for reasons such as extension of the recurrent nerve and crush injury of the recurrent nerve. Evaluating the recurrent nerves and improving the surgical procedure using NIM nerve monitoring systems is expected to help prevent recurrent nerve palsy^[23].

We consider dissection of the mediastinal lymph nodes using our MELD procedure to be sufficient. However, whether the mediastinal lymph nodes are truly sufficiently dissected using this approach should be confirmed in the next stage.

CONCLUSION

We conclude that a bilateral cervico-pneumomediastinal approach is useful for performing bilateral upper mediastinal lymph node dissection and esophagectomy.

DECLARATIONS

Authors' contributions

Conception and design of the study: Tokairin Y, Nagai K

Informed consent of the patients was obtained by Tokairin Y, Nakajima Y, Kawad K, Hoshin A, Okada T, Matsui T, Yamaguchi K

Drafting of manuscript: Tokairin Y

Revision and final manuscript: Tokairin Y, Nagai K

General supervision: Kinugasa Y

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained as appropriate.

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Original Article

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Standardization of bilateral upper mediastinal lymph node dissection using microanatomical concepts in minimally invasive esophagectomy

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Abstract

Aim: We have recently standardized upper mediastinal lymph node dissection (UMLND) based on microanatomical concepts in minimally invasive esophagectomy using a 4K ultra-high-definition (HD) system. In this study, the aim was to investigate the outcomes of microanatomy-based standardization using 4K ultra-HD for UMLND with the main focus on thoracoscopic operative time.

Methods: We have performed more than 500 cases of thoracoscopic esophagectomy in the prone position as minimally invasive esophagectomy. After about 400 cases of thoracoscopic esophagectomy in the prone position, we established the microanatomy-based standardization of UMLND using a 4K ultra-HD system. Two groups were analyzed: a pre-standardization group ($n = 100$) and a post-standardization group ($n = 100$). Furthermore, the change in our thoracoscopic operative time for all cases was analyzed using the moving average method.

Results: In the post-standardization group, the rate of surgeries performed by operators with less than 20 years' experience was significantly higher ($P < 0.001$). There were no significant differences in the number of mediastinal lymph nodes dissected, intraoperative blood loss and total postoperative morbidity rates between the two groups. The rate of recurrent laryngeal nerve palsy decreased to less than half (19.8% to 9.6%) ($P = 0.061$) and the thoracoscopic operative time decreased [232.0 (202.8-264.0) min to 209.0 (176.0-235.0) min] significantly



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($P < 0.001$) after standardization. The moving average showed a marked decrease of thoracoscopic operative time during the standardization phase.

Conclusion: Microanatomy-based standardization enabled quicker and more precise UMLD despite an increase in the number of surgeries performed by less experienced operators.

Keywords: Minimally invasive esophagectomy, lymph node dissection, microanatomy, thoracoscopic operative time, recurrent laryngeal nerve palsy

INTRODUCTION

Esophageal cancer (EC) is one of the most common gastrointestinal malignancies, mainly in Asian countries, and has a poor prognosis^[1]. Even today, primary treatment is still radical esophagectomy with regional lymphadenectomy^[2]. The surgical strategy for EC though has been shifting towards minimally invasive esophagectomy (MIE). Currently, thoracoscopic esophagectomy is the most common type of MIE. In 1992, the world's first thoracoscopic esophagectomy was performed in the lateral decubitus position^[3]. For a period of time after, thoracoscopic esophagectomy in the lateral decubitus position (TELP) was the standard in MIE, and much progress was made, especially in Japan^[4,5]. Although thoracoscopic esophagectomy in the prone position (TEPP) was reported slightly later than TELP^[6,7], this procedure had not been used for a while. However, in 2006, Palanivelu *et al.*^[8] reported about 130 cases of TEPP and showed both decreased operative time and the frequency of respiratory complications compared with TELP and open esophagectomy. It was also reported that the main reasons for TEPP's usefulness were due to the advantages of good exposure of the surgical field and improved ergonomics for the surgeon. Since then, TEPP has increasingly been adopted all over the world, including here in Japan, and there have been several reports of the tolerability and efficacy of this procedure^[9-12].

Upper mediastinal lymph node dissection (UMLND) remains the most important procedure in esophageal cancer surgery. However, this has also been the most difficult and time-consuming part, especially in TEPP. Although there have been technical reports about UMLND in TEPP, the longer thoracoscopic operative times and the higher recurrent laryngeal nerve (RLN) palsy rates of 10%-28% represent persistent challenges^[9,13,14]. Recently, progress in the development of endoscopic optical instruments [2K full high-definition (HD), 4K ultra-HD, and 3-dimensional] has been remarkable. Using them, we have been able to identify the fine microanatomy of membranes and layers that were not previously visualized, and there have been some reports on this new concept of surgical microanatomy and its usefulness in esophageal cancer surgery^[13-18].

In our institution, we have performed more than 500 cases of TEPP. Since reaching around 350 cases, we have been able to use a 4K ultra-HD system for our surgeries. Therefore, we started microanatomy-based standardization of UMLND using this endoscopically magnified view and established it when we reached around 400 cases. Previously, we have reported the concept of this standardization on the left side and its usefulness for safe and efficient surgery, especially for decreasing recurrent laryngeal nerve palsy rates^[19]. Concurrently, we have also standardized UMLND on the right side with the same concept as on the left within the same period.

The aim of this study was to investigate the outcomes of our microanatomy-based standardized procedure for UMLND on both sides using a 4K ultra-HD system, with a focus on decreasing operative time.

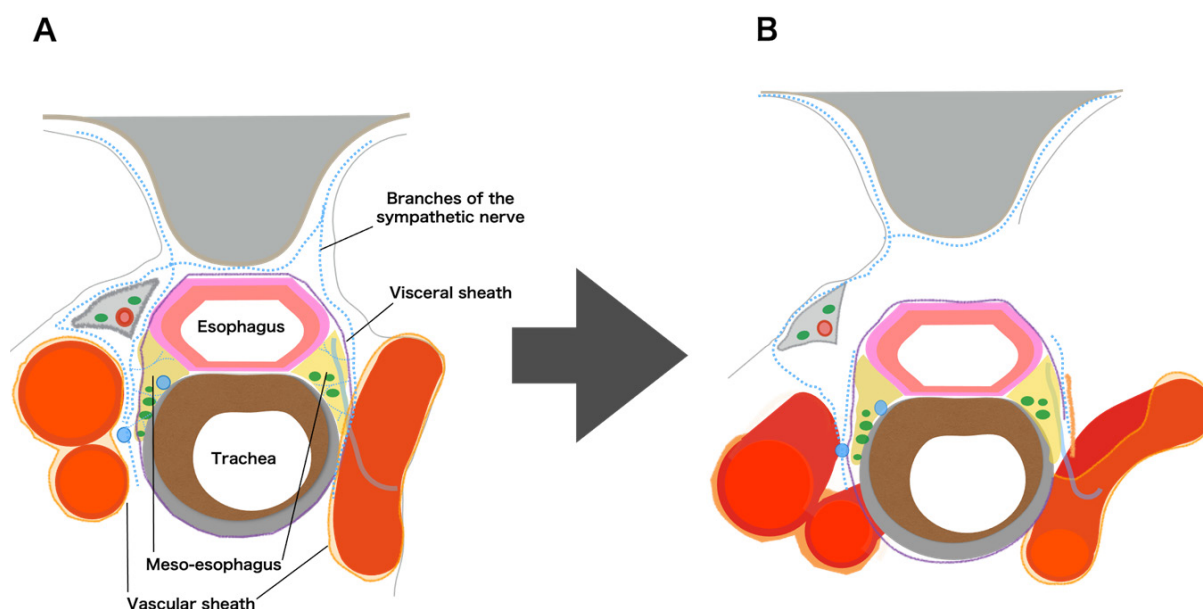


Figure 1. A: the microanatomical concept in the upper mediastinum; B: detaching the meso-esophagus while preserving the visceral sheath

METHODS

Patients

From June 2011 to January 2019, TEPP was performed in 500 patients (430 males, 70 females) with esophageal cancer at Okayama University Hospital. After reaching about 350 cases in April 2017, we started the microanatomy-based standardization of UMLND using a magnified view through a 4K ultra-HD system, and established it after reaching about 400 cases in November 2017. In this study, two groups were compared for the analysis: a pre-standardization group (100 cases up to completing 350 cases) and a post-standardization group (100 cases after completing 400 cases), as in our previous study^[19]. Cases with tumors invading surrounding organs (T4), with omission of UMLND, after thoracotomy, and cases of robotic surgery were excluded. Final analysis thus included 91 cases of the pre-standardization group, and 83 paired cases of the post-standardization group. This study was approved by the Ethics Committee of Okayama University Hospital (1811-009).

Procedure of TEPP

Positioning of the patient, placement of the thoracoscope and ports, and the basic procedure of TEPP were performed as previously reported^[19,20]. Since April 2017, a 4K ultra-HD camera system (IMAGE1 STM, Karl Storz, Tuttlingen, Germany and Visera 4K UHD, Olympus Corporation, Tokyo, Japan) has been used.

Microanatomy-based standardization of left upper mediastinal lymph node dissection

In our procedure, the concepts of the meso-esophagus and visceral sheath are important. The meso-esophagus contains the lymph nodes around the recurrent laryngeal nerve, and the visceral sheath wraps the esophagus, trachea, and bilateral meso-esophagus [Figure 1A]^[19]. First, we peel off the dorsal and lateral sides of the esophagus, preserving the visceral sheath. On the lateral side, adhesions around the visceral sheath are so tight that we always have to peel it off together with branches of the sympathetic nerve [Figure 1B and 3A]. Furthermore, on the right side, we also peel it off together with the vascular sheath [Figure 1B]. Next, we detach the esophagus and the meso-esophagus from the trachea and aggregate the lymphatic chain to the esophageal side [Figures 2A, D and 3B]. Next, we proceed with lymph node dissection along the recurrent laryngeal nerve from the central to the peripheral part. On the left side especially, we flip up the

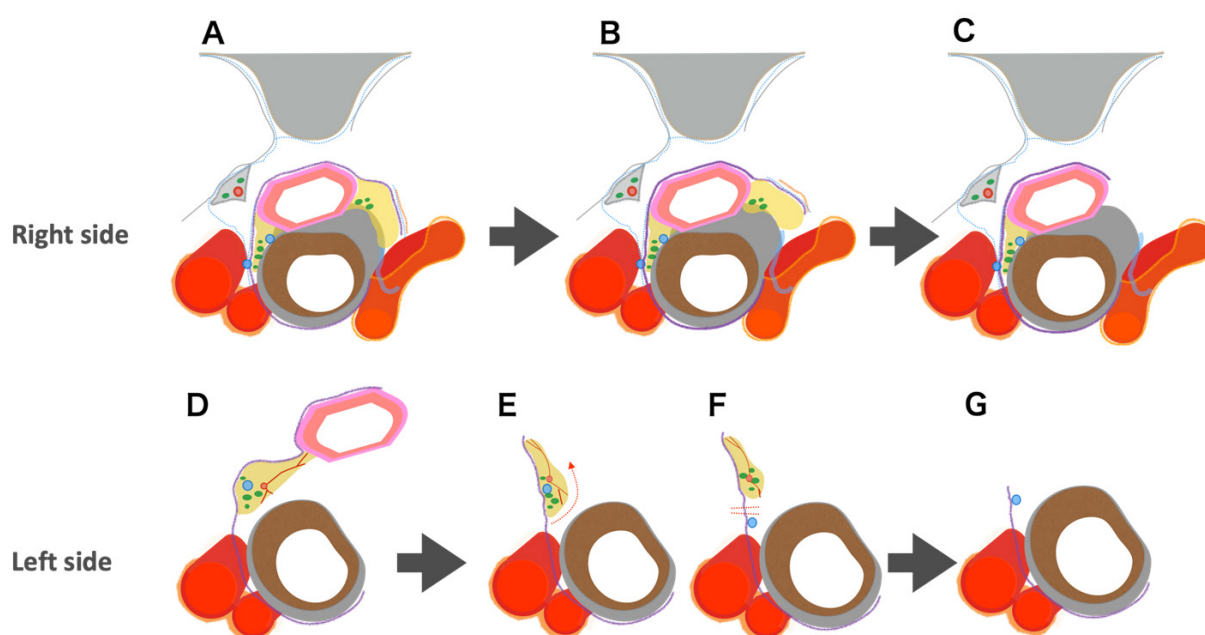


Figure 2. Microanatomy-based standardization of upper mediastinal lymph node dissection. A, D: detaching the esophagus together with the lymphatic chain from the trachea and aggregating the lymphatic chain to the esophageal side; B, E, F: identifying the recurrent laryngeal nerve and lymph node dissection along the nerve from the central part to the peripheral part; C, G: final findings of upper mediastinal lymph node dissection

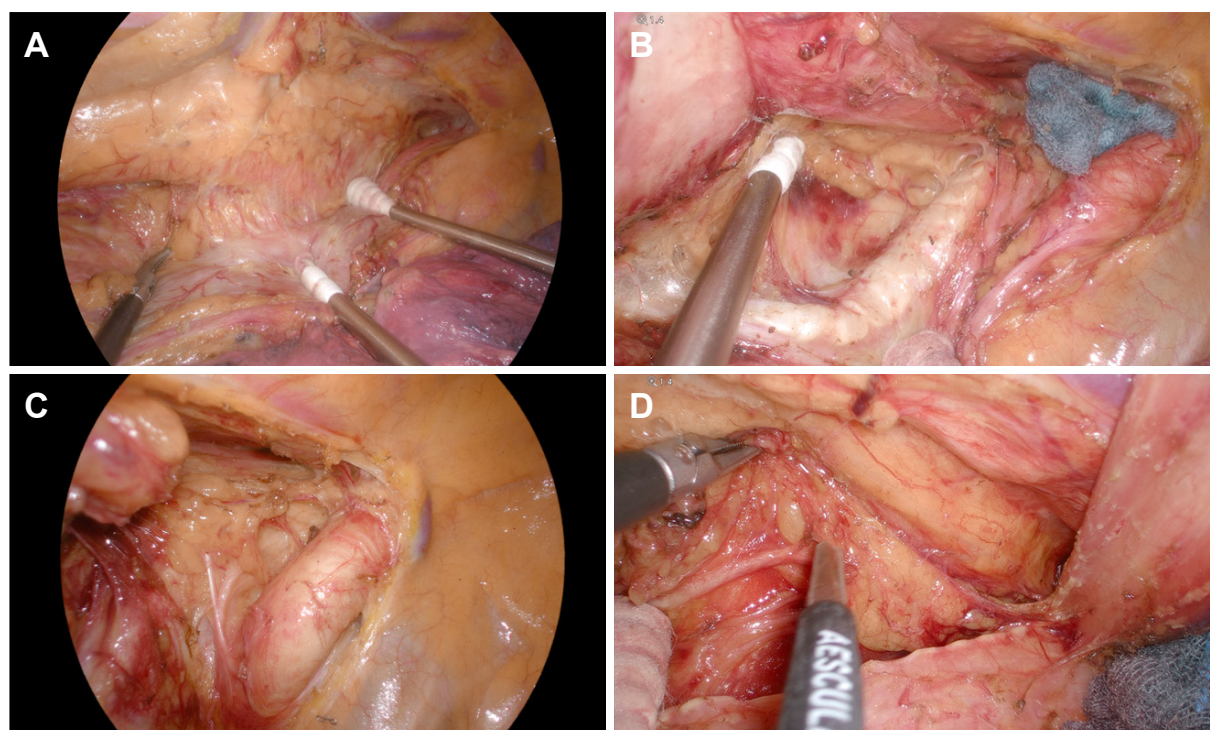


Figure 3. Thoracoscopic 4K ultra-high-definition view. A: detaching the meso-esophagus on the left side while preserving the visceral sheath; B: aggregating the lymphatic chain to the esophageal side on the left side; C: upper mediastinal lymph node dissection on the right side; D: upper mediastinal lymph node dissection on the left side

lymphatic chain on the inner surface of the visceral sheath and slide the nerve down to the natural position [Figures 2B, E, F and 3C, D]. Finally, we cut the visceral sheath on the dorsal side of the nerve [Figure 2C, G].

Table 1. Patients' characteristics

Characteristics	Total cohort		P value
	Pre-standardization group (n = 91)	Post-standardization group (n = 83)	
Age, median [years (IQR)]	67 (61-72)	67 (60-73)	0.744 ^a
Sex			
Male (%)	75 (82.4)	68 (81.9)	0.933 ^b
Female (%)	16 (17.6)	15 (18.1)	
BMI, median [kg/m ² (IQR)]	21.3 (19.6-23.2)	22.1 (20.3-23.5)	0.216 ^a
Neoadjuvant chemotherapy (%)	53 (58.2)	45 (54.2)	0.592 ^b
Clinical stage (UICC 8th)			
0, I, II (%)	55 (60.4)	51 (61.4)	0.892 ^b
III, IV (%)	36 (39.6)	32 (38.6)	
ASA-PS			
1 (%)	22 (24.2)	24 (28.9)	0.414 ^b
2 (%)	49 (53.8)	47 (56.6)	
3 (%)	20 (22.0)	12 (14.5)	
Tumor location			
Ce (%)	5 (5.5)	6 (7.2)	0.292 ^b
Ut (%)	9 (9.9)	17 (20.5)	
Mt (%)	46 (50.5)	36 (43.4)	
Lt (%)	23 (25.3)	20 (24.1)	
Ae (%)	8 (8.8)	4 (4.8)	
Histological diagnosis			
SCC (%)	82 (90.1)	76 (91.6)	0.099 ^b
ADC (%)	6 (6.6)	4 (4.8)	
Others (%)	3 (3.3)	3 (3.6)	
Lymph node dissection			
Two-field dissection (%)	49 (53.8)	34 (41.0)	0.089 ^b
Three-field dissection (%)	42 (46.2)	49 (59.0)	
Operator experience			
≥ 20 years (%)	61 (67.0)	22 (26.5)	< 0.001 ^b
< 20 years (%)	30 (33.0)	61 (73.5)	

^aMann-Whitney test, ^b χ^2 test. IQR: interquartile range; BMI: body mass index; Ce: cervical esophagus; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; SCC: squamous cell carcinoma; ADC: adenocarcinoma

Description and statistical analysis

Clinicopathological factors were noted according to the Japanese Classification of Esophageal Cancer^[21,22] and the Union for International Cancer Control TNM Classification of Malignant Tumors, 8th edition^[23]. Postoperative complications were categorized using the Clavien-Dindo classification^[24] [Table 1]. To evaluate differences between the two groups, continuous variables were assessed using the Mann-Whitney test, and categorical variables were assessed using the χ^2 test or Fisher's exact test. Differences were considered significant when *P* values were < 0.05. All analyses were performed using JMP version 14 statistical analysis software (SAS Institute, Cary, NC, USA). The thoracoscopic operative time learning curve was analyzed using the moving average method^[25,26]. With the moving average method, using the mean of thoracoscopic operative times, the trends are clarified and the changes are smoothened. A 20-case moving average was used in this study, and the exclusion criteria of the cases were the same as above.

RESULTS

Patients' characteristics

There were no significant differences in patient characteristics between the two groups [Table 1]. On the other hand, the rate of surgeries performed by operators with less than 20 years' experience was significantly higher in the post-standardization group (*P* < 0.001).

Table 2. Surgical findings

Variable	Pre-standardization group (n = 91)	Post-standardization group (n = 83)	P value
Intraoperative findings			
Thoracoscopic operative time [min (IQR)]	232.0 (202.8-264.0)	209.0 (176.0-235.0)	< 0.001 ^a
Blood loss [mL (IQR)]	200 (100-330)	200 (105-400)	0.764 ^a
Number of dissected No. 106 lymph nodes (IQR)	11 (8-15)	10 (8-13)	0.137 ^a
Conversion to thoracotomy (%)	0 (0)	0 (0)	1.000 ^b
Postoperative findings			
Total morbidity [≥ Grade II (%)]	48 (52.7)	37 (44.6)	0.250 ^b
Respiratory complications [≥ Grade II (%)]	15 (16.3)	14 (16.9)	0.946 ^b
Recurrent laryngeal nerve palsy [≥ Grade I (%)]	18 (19.8)	8 (9.6)	0.061 ^b
Anastomotic leakage [≥ Grade II (%)]	7 (7.7)	9 (10.8)	0.472 ^b
ICU stay [days (IQR)]	6 (5-7)	6 (5-6)	0.742 ^a
Postoperative hospital stay [days (IQR)]	21 (17-26)	22 (17-27)	0.782 ^a
In-hospital mortality (%)	0 (0)	0 (0)	1.000 ^b

^aMann-Whitney test, ^b χ^2 test. Complications are described according to the Clavien-Dindo classification^[24]. IQR: interquartile range; ICU: intensive care unit

Clinical outcomes

There were no significant differences between the two groups in the amount of blood loss during surgery, and the number of dissected lymph nodes around the recurrent laryngeal nerves (No. 106). In both groups, no patients required conversion to open thoracotomy [Table 2]. There were no significant differences in total morbidity rate, the incidence of respiratory complications or anastomotic leakage (≥ Grade 2). Regarding RLN palsy, vocal cord motility was checked in all patients by endoscopy on postoperative day 1, and any dysmotility was defined as RLN palsy (≥ Grade 1). The incidence of RLN palsy decreased to less than half (19.8% to 9.6%) after standardization ($P = 0.061$) [Table 2]. There were also no significant differences in ICU stay and postoperative hospital stay, and there were no postoperative mortalities in either group.

Change in thoracoscopic operative time

There was a significant difference in thoracoscopic operative time between the pre-standardization group and the post-standardization group [$n = 91$, 232.0 (202.8-264.0) min vs. $n = 83$, 209.0 (176.0-235.0) min, ($P < 0.001$)] [Table 2]. The moving average curve showed that the thoracoscopic operative time decreased markedly during the phase of microanatomy-based standardization of UMLD (from 350 cases to 400 cases) and stabilized [Figure 4].

DISCUSSION

When most MIEs were performed via TELP, there were reports that precise mediastinal lymph node dissection by MIE was as feasible as that by open thoracotomy with the added advantages of lesser decrease in respiratory function and lower respiratory complication rates^[4,5]. However, even now, it is important in TELP to have a special team composed of three experts (i.e., surgeon, assistant, and endoscopist) to perform the procedure smoothly. On the other hand, an excellent surgical field contributed simply by gravity and artificial pneumothorax without the need for an assistant is one advantage of TEPP. Furthermore, the improved ergonomics for the surgeon in TEPP is another advantage.

In the early phase of introducing TEPP in this decade, there were some reports about its conferred advantages for lymph node dissection, especially in the upper mediastinum^[9-12]. Along with the recent, remarkable progress of endoscopic optical instruments such as 3D and 4K ultra-HD, there have also been reports about the microanatomy-based surgical concept for MIE, similar to total meso-rectal excision in rectal cancer surgery^[13-18]. More recently, we have established the microanatomy-based standardization using the concept of the meso-esophagus wrapped with the visceral and vascular sheaths and reported

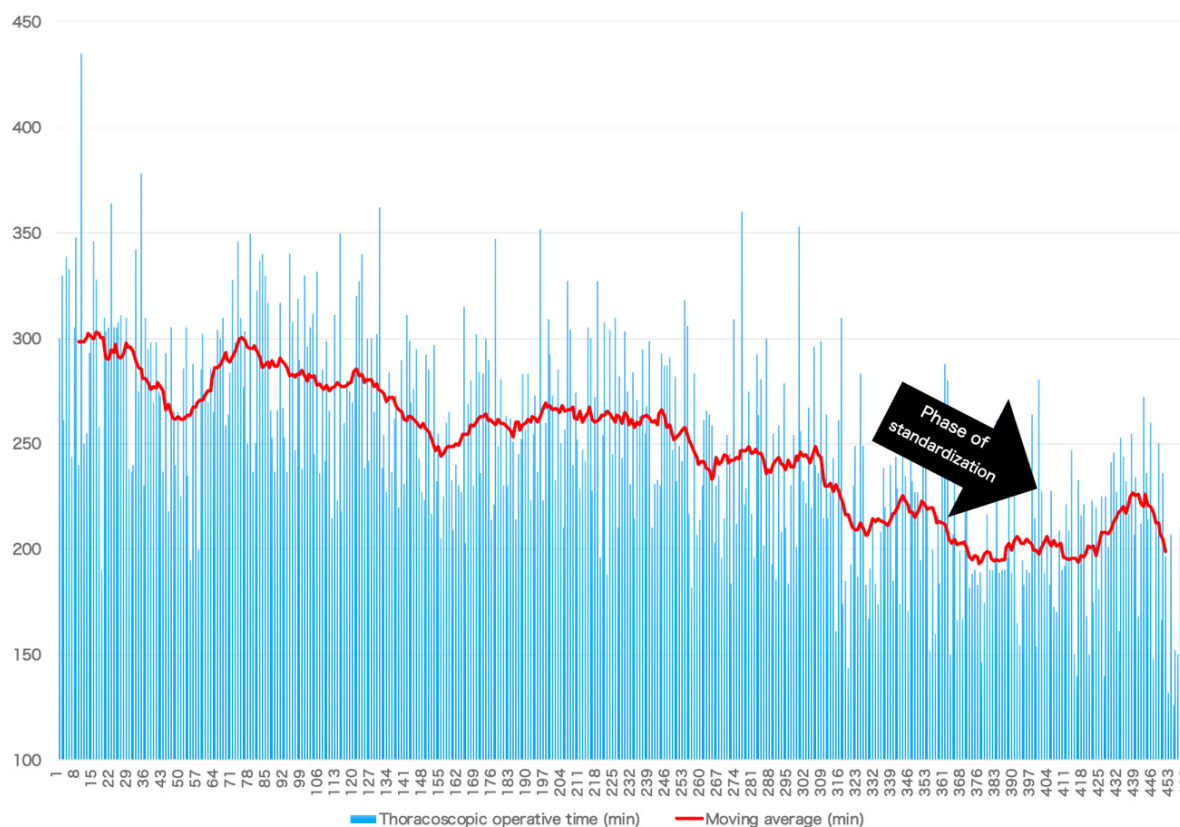


Figure 4. Twenty-case moving average of thoracoscopic operative time

its usefulness for left UMLND^[19]. Although we thought that this concept could also be applied for right UMLND, the asymmetrical anatomical structure in the upper mediastinum was an issue. The branching patterns of the arteries are different and the points of recurrence of the recurrent laryngeal nerves and their running direction and length are also different. However, for both the right and left sides, the recurrent laryngeal nerves originate from each main trunk of the vagal nerve within the vascular sheath and transit to the inner aspect of the visceral sheath after turning back at an artery. The nerves then run to the larynx as their target organ through the meso-esophagus. In addition, lymph nodes around the recurrent laryngeal nerve that should be dissected as regional lymph nodes are located within the meso-esophagus on both sides. In the first step of our standardization of UMLND, it is most important not to destroy the visceral sheath enveloping the lymphatic chain in the meso-esophagus, although the vascular sheath on each side should be detached in a different manner and range. After that, we proceed to en bloc lymph node dissection while preserving the visceral sheath and nerve.

Regarding thoracoscopic operative time, the first learning curve occurred due to the initial standardization of the lower mediastinal procedure of TEPP^[20]. After the initial standardization, the indication was expanded for thoracoscopic surgery. The thoracoscopic operative time again lengthened, followed by a second gentle, natural learning curve. However, after that, no obvious learning curve effect was achieved until more than 300 cases. Nevertheless, the microanatomy-based standardization during this time from case 350 to 400 contributed to a marked decrease in thoracoscopic operative time (by almost 30 min), even though the number of surgeries performed by less experienced operators increased. We believe that accurate understanding of the microanatomy involved contributed towards defining the surgical planes more easily for quick dissection of tissues including the lymph nodes without extra bleeding. On the other hand, young surgeons could also learn the microanatomy from experienced surgeons through

the clear 4K HD images and could re-watch the operation many times. Furthermore, there was also a concurrent decrease in postoperative complication rates. Therefore, our microanatomy-based concept appears to be useful not only for accurate and quick UMLD, but also for young surgeons to master the procedure efficiently.

Now, in our institution, we can conduct three types of MIE [thoracoscopic surgery, mediastinoscopic surgery, and robotic-assisted surgery (RAMIE)], and the rate of RAMIE has recently been increasing. We believe that RAMIE is an advanced form of thoracoscopic surgery and our microanatomy-based standardization approach could be similarly applied. Furthermore, we expect that this standardization will make much progress using the joint function and shake reduction system unique to RAMIE.

In conclusion, microanatomy-based standardization using a 4K ultra-HD system enabled quicker and more precise UMLD despite an increase in the number of surgeries performed by less experienced operators.

DECLARATIONS

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Establishment of study materials or enrolment of patients: Shirakawa Y, Noma K, Tanabe S, Sakurama K, Fujiwara T

Data scrutiny, analysis, and clarification: Shirakawa Y

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Study supervision: Fujiwara T

Read and agree with the final manuscript: Shirakawa Y, Noma K, Maeda N, Tanabe S, Sakurama K, Fujiwara T

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Review

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Transanal total mesorectal excision for rectal cancer: state of the art

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Abstract

Total mesorectal excision remains the gold standard for surgical treatment for rectal cancer to achieve excellent oncological outcomes. The transanal approach to the mesorectum was introduced to complement conventional surgery so that technical difficulties related to the distal rectal dissection could be overcome. Since its introduction, interest in transanal mesorectal excision has been growing and it appears that the benefits are maximal in patients with mid-low rectal cancer where anatomical and pathological factors present the greatest challenges. Current evidence demonstrates this approach is safe and feasible, with an acceptable morbidity profile, but with specific complications related to the technique. Oncological and functional data seem comparable to the conventional approaches, but most of the results come from small studies with short-term endpoints. Robotics, when available, might potentially overcome the difficulty of distal rectal dissection with a shorter learning curve compared to the transanal approach, but with higher costs. The aim of this review is to critically evaluate the available literature concerning transanal total mesorectal excision so that we can better define its role in the management of rectal cancer.

Keywords: Rectal cancer, total mesorectal excision, transanal total mesorectal excision, transanal surgery, laparoscopy

INTRODUCTION

Total mesorectal excision (TME) remains the gold standard approach to the surgical treatment of rectal cancer^[1]. The application of this key technical principle has represented a revolution in rectal cancer



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surgery, demonstrating how the integrity of the mesorectal envelope is paramount in achieving excellent oncological outcomes in terms of local recurrence^[2]. Minimally invasive techniques have shown major benefits in the treatment of colon cancer, but rectal surgery is technically more demanding and the associated steep learning curve has made the laparoscopic approach less appealing.

Nevertheless, surgical techniques are constantly evolving and searching for less invasive approaches, particularly pursuing the principles of natural orifice transluminal endoscopic surgery (NOTES) represents an exciting goal. A further reduction in postoperative pain, less wound infections and hernias, better cosmetic results and a shorter time off work are the key advantages of these super-minimally invasive approaches^[3,4].

It is suggested that bulky colorectal specimens can be effectively excised transanally^[5] and several experimental studies have demonstrated the safety and feasibility of rectosigmoid transanal resection in animal and cadaveric models^[6,7].

Pure NOTES still requires significant improvement in instruments and technology to make the transition to the clinical arena and remains largely an experimental approach, while hybrid procedures such as natural orifice specimen extraction (NOSE) techniques combined with laparoscopy can reduce the impact of surgery further^[5,7,8].

As a result of these experiences, the first transanal rectal resection with a hybrid approach was described by Sylla *et al.*^[7] in a 76-year-old lady with a rectal cancer located at 8 cm from anal verge.

This first report, describing transanal TME (TaTME), aroused great interest because it demonstrated the feasibility of a hybrid NOTES procedure that could be applied to challenging real-life situations, such as the difficult TME for mid and distal rectal cancer.

Indeed, even in the hands of experts, rectal cancer surgery in obese, male patients with bulky, distal tumors can be extremely difficult, where the ballooning of rectum into the sacral concavity creates a sharp angle with the anal canal^[9]. In these cases, difficulty in staying in the correct dissection plane can easily result in an incomplete specimen with possible inadequate circumferential resection margin (CRM)^[10].

Despite the standardization of technique for TME, several studies have demonstrated that the quality of the final specimen is important in predicting cancer-related outcomes^[11,12]. Obese patients with low, anteriorly-located tumors, those treated with neo-adjuvant chemoradiotherapy, or those with a narrow pelvis are at particular risk of incomplete mesorectal excision^[13-15].

Laparoscopy offers the advantage of improved visualization of deep pelvic structures, but the limitations imposed by long and straight instruments, particularly applying traction and counter-traction maneuvers in a narrow space, remain significant challenges. In addition, laparoscopic stapling technology has proved rather inadequate and difficult to use low in the pelvis, increasing the risk of poor outcomes^[16,17].

TaTME was conceived and developed with the aim of overcoming these specific limitations, particularly in mid and low cancers. The closer, more detailed view of the pelvic structures makes the dissections from below more accurate and effective, leading to a better specimen. Inserting the purse-string below the tumor allows the surgeon to accurately control the distal resection margin (DRM). In the case of anterior tumors, with a high risk of an involved circumferential margin, the transanal approach can facilitate the dissection of Denonvilliers fascia, thus minimizing the risk of injuries to prostate, seminal vesicles, and the nerves of the inferior hypogastric plexus and nervi erigentes.

Because of these potential advantages, TaTME has gained wide interest in the colorectal community and represents an opportunity to improve patient outcomes; however, it remains a technically challenging operation and further research is required to prove its oncological efficacy when more widely adopted.

DEVICE AND TECHNIQUE

In 1983, Prof. Gerard Buess conceived transanal endoscopic microsurgery (TEM) and, in cooperation with Richard Wolf, created and developed the platform for endoscopic rectal surgery, with the aim to treat benign lesions of the upper and middle rectum not previously reached with conventional transanal approaches^[18,19].

Based on this model, the Transanal Endoscopic Operation (TEO; Karl Storz, Tuttlingen, Germany) was developed, which provides a rigid operative rectoscope, compatible with many standard laparoscopic instruments without the need for a dedicated platform.

In 2009, in Orlando, Florida, Atallah and colleagues introduced the concept of transanal minimally invasive surgery (TAMIS). This was inspired by devices already created for single-site surgery in the abdomen but were adapted for transanal access. This essentially created a flexible, transanal multiport device that could be used with a conventional laparoscope and laparoscopic instruments^[20].

To date, two transanal platforms, GelPoint Path (Applied Medical, Rancho Santa Margarita, Ca) and SILS Port (Covidien, Mansfield, Ma), have gained FDA approval for TAMIS. Clinical studies published thus far demonstrate that both these and rigid platforms such as TEM/TEO can be used for TaTME, but the review by Araujo *et al.*^[21] shows that only the 24.7% (37/150) of the preliminary TaTME cases reported were performed with a platform TEM/TEO.

TAMIS ports have now become the preferred option for surgeons dedicated to TaTME because, compared to rigid platforms, the soft, flexible port offers more versatile access to the whole circumference of the rectal lumen without multiple position changes during surgery, the equipment is quicker and easier to set up, and there may also be economic advantages^[22,23].

With improving experience and the dissemination of this approach through research and training, many different technical modifications have been introduced, although the cardinal principles of this procedure remain the same: to provide a complete mobilization of the mesorectum from the pelvic floor upwards according to the eight steps described by Whiteford and colleagues in 2007^[24].

TaTME can be performed either with two different surgical teams working simultaneously with abdominal and transanal dissection or with a two-step approach, using the same surgical team for both operative phases in sequence.

Abdominal phase: the abdominal phase is performed according to the standard approach and preference of the operating surgeon. It should be noted that either a planned open approach or a laparoscopic conversion does not preclude a transanal approach to the pelvis. If a sequential approach is used (usually due to the lack of two operating teams being available), then transabdominal dissection proceeds into the pelvis along the mesorectal fascia until it becomes technically challenging and the specimen or the surrounding key pelvic structures are at risk. Even in extremely challenging cases, the peritoneum will be divided anteriorly before changing to a transanal approach as this will facilitate entry into the abdominal cavity from below. Abdominal pneumoperitoneum is deflated, the insufflator is turned off, and the ports are closed prior to the legs being positioned for the transanal phase.

Transanal phase: the transanal phase commences with a digital rectal examination to ensure the rectum is empty and that the clinical findings correlate with the MRI scan. The placement of a self-fixing anal retractor (Lone Star CooperSurgical, Trumbull, CT, USA) may be useful to better expose the anal canal, particularly in male patients with a long anal canal. Insertion of the transanal platform should reveal distal rectal mucosa through the anal channel. Fixation of the TAMIS port to the anal margin, positioning of the ports in the gel-cap with attachment, and gentle insufflation will facilitate clear views and safe operating. Initial laparoscopic inspection will allow assessment of the height of the tumor from anal verge in order to plan the positioning of the purse-string and the rectotomy.

A purse-string suture is placed at least 10 mm distal to the tumor to seal the rectal lumen, and then rectal irrigation eliminates debris and prevents the possible implantation of free cancer cells.

Carbon dioxide is insufflated into the distal rectal lumen to obtain a stable pneumorectum with a pressure of 10-20 mmHg and the rectal mucosa is marked circumferentially with monopolar hook. A full thickness rectotomy is started, usually posteriorly where the plane between presacral fascia and mesorectum is more easily identified, but slightly laterally where the ano-coccygeal ligament is less easily encountered.

The rectal transection is performed by opening the different layers of the rectal wall until the mesorectal plane is identified. Once the whole circumference of the distal rectal wall has been divided, the rectal specimen will retract upwards slightly, revealing the posterior mesorectal fascia. At this stage, the closed purse-string can be reinforced with a second V-LocTM suture (Covidien, Mansfield, Ma) to reduce the risk of intraluminal leakage during the pelvic dissection. The posterior plane is developed first, anterior to the pre-sacral fascia and along the angel hair of the mesorectal fascia which is kept intact. The anterior plane is approached afterward, keeping the dissection in front or behind Denonvillier's fascia according to the rectal cancer position. The lateral dissection can then proceed, using the areas of correct dissection from the front and back to guide the dissection; this will minimize the risk of injuries to the neurovascular structures laterally and antero-laterally. Mesorectal dissection should proceed in a cylindrical fashion avoiding distortion of the specimen. Entry into the abdominal compartment should be delayed as late as possible, as accurate mesorectal dissection is impaired once a communication is established between the two cavities. When the dissection is complete, a careful assessment is made of whether the specimen can be safely extracted transanally or not, considering the size of both the specimen but also the stage of the cancer. The length of the remaining distal rectal cuff will determine whether a hand-sewn anastomosis will be required or whether there is adequate tissue for a distal purse-string to be inserted in preparation for a stapled anastomosis. Distal purse-strings can be inserted laparoscopically or as an open procedure with the TAMIS port still in-situ but drawn distally to stent the anorectal lumen or with the TAMIS port removed and the Lone Star retractor giving access. Various methods of stapled anastomosis techniques have been described^[25].

Techniques to assess the vascular supply to the anastomosis have been described^[26], but one of the benefits of TaTME is direct inspection and palpation of the whole circumference of the anastomosis prior to the end of the operation. This may allow selective defunctioning stomas to be performed according to individual patient risk factors.

INDICATIONS

Ideal candidates for TaTME are patients with mid or low rectal cancer (within 10 cm from the anal verge), especially in male patients (because of the narrow pelvis or prostate hypertrophy/previous prostate surgery), obesity, bulky tumors, or after neoadjuvant radiotherapy, and, for these reasons, this approach may have the most to offer these patients. The San Gallen Consensus concurs that TaTME may be technically easier compared to abdominal techniques in this group of patients^[27].

Current practice suggests that selection of patients for TaTME includes a wider group of patients, particularly with regard with tumor location, as we can observe with the experience of Lacy or in the International Registry where tumors were proximally located in 20.7% and 38% of patients, respectively^[28,29], however this remains primarily a technique for those requiring TME.

Appropriate patient selection is of paramount importance, especially during the early learning curve and it is wise not to select very difficult cases before competence is reached. In this respect, expanding the indications for TaTME to include those patients who could easily be done laparoscopically may be required for training purposes.

PERIOPERATIVE RESULTS

Feasibility and safety of perioperative outcomes of TaTME have been extensively reported as well as limitations and shortcomings that need to be addressed.

Reduced estimated blood loss, shorter hospital stay, and lower readmission rates were recently reported in a meta-analysis of 17 studies^[30].

Compared to laparoscopic TME, a lower rate of conversion to open surgery has been observed, ranging between 0% and 9.1%^[22,31,32]. This correlated to the level of experience, as highlighted by Deijen and colleagues who compared low-volume centers performing TaTME (< 30 cases) to high-volume centers (> 30 cases) and reported conversion rates of 4.3% and 2.7%, respectively^[33].

Conversions during TME surgery are usually due to technical difficulties related to high body mass index (BMI) and the narrow male pelvis. Ma *et al.*^[32] showed that this accounted for 25% of conversions in TaTME patients *vs.* 47% in those undergoing laparoscopic TME. In most reported series, the occurrence of intraoperative complications provoke conversion, with tumor or patient features not directly affecting the operation outcome.

TaTME has also been shown to have a significantly shorter operation time, compared to laparoscopy^[34], and this is even more pronounced if the operation is performed with a simultaneous two-team approach^[35].

Concerning morbidity, several retrospective series or cohort studies reported on safety of TaTME, showing postoperative complication rates comparable with conventional laparoscopic or open TME data^[36].

The international TaTME registry including 720 patients reported an overall morbidity of 32.5%^[29], in line with several other monocentric series on TaTME^[22,37].

In a recent systematic review, TaTME and laparoscopic TME showed similar rates of intraoperative complications, although a lower rate of postoperative morbidity was reported in the transanal group^[32].

Several publications report a low incidence of anastomotic leak rate following TaTME, which in the largest meta-analyses available ranges between 5.7% and 6.1%^[33,38] and is similar to the results reported after conventional TME^[39].

Recently updated data from the multi-institutional International TaTME registry on 1594 patients over 30 months show an overall 30-day anastomotic leak rate of 7.8%^[40], not too far from the rate of 10% reported by Ma *et al.*^[32] in their systematic review.

Finally, the potential for major bacterial contamination as a consequence of the rectal transection, as shown by Velthuis with 39% of positivity of pelvic culture, suggests the risk for higher rates of pelvic sepsis, but this concern was not confirmed by subsequent studies^[41].

Indeed, the literature available reports an average rate of pelvic abscess of 2%-3%^[29,42] and more up to date review data confirm an overall incidence of 2.2%^[33].

Despite these encouraging results, TaTME has some very specific complications. Rouanet reported urethral injury in 6.6% of cases; however, this was a series of 30 difficult high BMI male patients, most following radiotherapy^[43]. However, urethral injury is a serious complication directly related to the transanal phase of the operation and is very uncommon during open or laparoscopic TME.

In the largest multi-institutional registry reporting on 720 patients, the occurrence of urethral injuries was 0.7% and was associated with bladder injuries, vaginal and rectal perforations, and damage to hypogastric nerves^[29].

Another matter of concern specific of this technique is the possibility by pneumo-pelvis of creating a false dissection plan, misleading the surgeon and increasing the risk of inadvertent damages of sidewall autonomic nerves and vessels laterally and of sacral venous plexus posteriorly^[29].

Finally, carbon dioxide embolism during TaTME, a rare but potentially life-threatening complication, was reported by Ratcliffe *et al.*^[44] and may occur in up to 0.4% of patients, mandating conversion to open and giving rise to postoperative morbidity^[45].

ONCOLOGICAL RESULTS

TaTME was conceived to overcome some of the technical challenges in rectal cancer surgery, enabling dissection of a high quality mesorectal envelope. Soon after its introduction, several preliminary reports showed a good quality mesorectum in almost all cases, negative circumferential and distal margins, and a level of lymph node harvesting comparable with the conventional approach^[37,46,47].

These results are important since an incomplete TME represents an independent risk factor for local recurrence, regardless of the achievement of circumferential and distal negative margins^[48].

With an intact mesorectal fascia, the likelihood of local recurrence, even with involved lymph nodes, is significantly lower than with a threatened one and is around 7.5%^[49].

Negativity of circumferential margin^[45] is another indicator of the quality of the rectal resection and its involvement is reported in 8%-10% of cases^[50].

Fernández-Hevia *et al.*^[22] confirmed this trend by comparing TaTME with laparoscopy in a match-controlled study showing similar numbers of lymph nodes harvested and negative circumferential margin in all cases.

Velthuis obtained similar results demonstrating that with a transanal approach a significantly higher rate of complete mesorectal excision could be achieved, compared with laparoscopic patients^[51].

In an early meta-analysis reporting data on 510 patients, a complete TME specimen was reported in 88% of cases and near complete in 6%, while CRM was positive in 5% of cases and the DRM in 0.3% of cases^[38].

Hu *et al.*^[52] showed that a complete mesorectal excision rate was 1.93 higher in the TaTME compared to laparoscopic TME, with a lower positive CRM rate, while positive DRM rate did not reach statistical difference.

Recently, in 513 TaTME procedures performed in the UK, optimal pathology was observed in 295 patients (92.8%), with an involved resection margin (R1) in 13 patients (4.1%)^[53].

Can these preliminary short-term pathological advantages translate into the final target of a lower recurrence rate?

Lelong *et al.*^[54] in a comparative series including 72 patients, with a median follow-up period of 31.9 months, demonstrated similar results following laparoscopic or TaTME (5.3% and 5.7% local recurrence rate, respectively), but, considering only patients with curative resections (no metastases at diagnosis), local recurrence rates were 5.7% and 0%, respectively.

A two-center experience of 159 TaTMEs procedures showed the 3- and 5-year local recurrence rates were 2% and 4.0%, respectively, with a median time to local recurrence of 19.2 months (range 5.9-30.0 months)^[55].

On the other hand, the Norwegian Colorectal Cancer Group expressed a warning against this technique, reporting a 9.5% rate of early local recurrence with rapid, multifocal growth in the pelvic cavity and sidewalls, and a median time to recurrence of 11 months. The observed local recurrence rate following laparoscopic TME was 3.4%^[56].

The small sample size of the experiences published thus far underline the need for a larger multicenter RCT for TaTME to better assess the long-term oncological results compared to conventional techniques.

FUNCTIONAL RESULTS

Bowel, sexual, and urinary dysfunction is common after rectal cancer surgery and is associated with social and psychological impairment. Anorectal disturbance can be caused by sphincter damage, reduced capacity of the neo-rectum, level of anastomosis, pelvic nerve damage, and the effects of radiotherapy. Up to one third of patients experience “anterior resection syndrome”, which is characterized by functional disorders such as urgency, increased bowel frequency, fragmentation, and incontinence. A similar proportion experiences genitourinary problems, including impotence and retrograde ejaculation in men and sexual dysfunction in both sexes.

The relationship between these functional complaints and the quality of life perception is difficult to establish and poorly reported in the literature. In general, major bowel and urinary alterations affect social functioning, while incontinence and fecal urgency also impact on mental health.

With acceptable perioperative and oncological results, functional outcome and quality of life measures after TaTME represent important outcomes for patients.

The transanal approach for low rectal cancer has not been shown to significantly increase bowel and urologic dysfunction, compared to conventional laparoscopy, but may be associated with better erectile function with a significantly higher rate of sexual activity^[57,58]. Quality of life and functional outcomes, assessed by validated questionnaires, showed acceptable outcomes after TaTME at 6 months after surgery^[59].

Rubinkiewicz *et al.*^[60], in a comparative study concerning the occurrence and severity of low anterior resection syndrome, reported similar results between TaTME and LaTME, with a prevalence still high in both groups (87% and 91%, respectively).

Assessment of patients after TaTME by transanal endoscopic ultrasound and physiological functional assessments concluded that TaTME has no impact on sphincter structure and evacuatory function, with about 10% of patients with major low anterior resection syndrome after 1 year^[61].

In conclusion, TaTME does not appear to increase the negative impact on functional and quality of life outcomes if compared to conventional laparoscopic transabdominal TME. Existing data concerning anorectal, urinary, and sexual function and quality of life following TaTME are still of low quality and further studies are needed in this area.

ROBOTIC TaTME

Robotic approaches can overcome several of the technical difficulties associated with traditional laparoscopic surgery and allow high-quality maneuvers to be performed in narrow spaces such as the pelvic cavity. Recent studies demonstrate similar clinical and oncological results between robotic and laparoscopic transabdominal surgical procedures^[62], but, at present, no significant benefit of robotic over laparoscopic surgery seems to be detectable, except perhaps conversion rates.

The application of robotic technology to TaTME (rTaTME) appears to be the next logical step in the evolution of minimal access surgery, allowing the benefits of improved dexterity, stability of the platform, and 3D-vision, while adhering to the principles of NOTES.

Small rTaTME case series have been reported demonstrating feasibility. Kuo *et al.*^[63] described a combined rTaTME and transabdominal single-site plus one port approach in 16 patients with low rectal lesions, showing good oncological results.

More recently, Hu *et al.*^[64] published a case series of 20 patients treated with r-TaTME with simultaneous laparoscopic-assisted abdominal phase performed with single-port placed at ileostomy site, demonstrating the applicability of this approach, but also highlighting some of the limitations of the Da Vinci Xi platform for transanal surgery.

The introduction of the robotic platform based on the single-port access may represent the start of a new era for robot-assisted transanal surgery, but ultimately smaller, more flexible robotic systems are required for true natural orifice procedures where scars are eliminated. If this can be combined with cost control, then a new era in surgery will be possible.

CONCLUSION

TaTME has demonstrated some tantalizing benefits for the surgeon and the patient, but remains controversial because of the lack of long-term oncological data and the technical operative challenges that make widespread dissemination difficult.

Some consider TaTME as the culmination of 30 years of progress in colorectal cancer surgery^[65]. Others, while applauding the results achieved to date, introduce a note of caution in their interpretation of the available data, as the majority of the published experience originates from highly trained surgeons in high-volume centers with great heterogeneity among studies^[66]. It is important that we avoid the indiscriminate adoption by inadequately trained surgeons that could undermine the progress achieved thus far^[67].

The debate will continue as to whether this should be an operation that is used selectively for the most difficult cases - in which case, expect worse outcomes - or whether it is a panacea to improve all rectal cancer surgery and therefore outcomes more widely^[43,46].

The distal third of the rectum remains challenging even in highly experienced surgical hands^[68] and could be difficult to reach transabdominally, sometimes at the price of an unavoidable derogation to principles of oncological radicality and nerve preservation. Even Bill Heald, the master of TME, in very challenging conditions used manual dissection to get out of otherwise impossible situations^[69].

For this reason, Heald himself has embraced and supported this conceptual revolution, considering the pneumodissection and the vision from below of great help in the challenging steps of the distal dissection, mainly on the anterior plane in the male pelvis, with a consequent better identification and preservation of nerves. Excited by Lacy's message, he considered it as the future of rectal cancer surgery^[70].

With similar postoperative complications when compared to standard laparoscopic or open TME, remarkable short-term pathological and surgical results, and promising long-term oncologic outcomes, the available literature suggests that TaTME is safe and feasible in the hands of surgeons who have had proper training and been supported through the early learning curve. If this technique is to be widely adopted, then formal training programs with adequate resources will have to be available to facilitate wider adoption without the increase in complications^[71].

The multicentric randomized controlled trial COLOR III, designed to compare TaTME and Laparoscopic TME is currently underway and will produce more reliable evidence concerning the quality of this type of surgery.

If the results already demonstrated are confirmed, TaTME should be considered among the gold standard approaches to be offered to selected high-risk patients with rectal cancer.

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Authors' contributions

Substantial contributions to conception and draft of the manuscript: De Rosa M, Wynn G, Rondelli F
Critical revision: Ceccarelli G, Wynn G

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Review

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Quality of life, pain, and functional respiratory recovery after lobectomy for early stage non-small cell lung cancer: a review of the literature comparing minimal invasive and open procedures

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Abstract

The recent improvement in surgical techniques for non-small cell lung cancer enables evident better results in term of postoperative recovery with lower adverse events. Even though the interest in minimally invasive procedures has increased, more subjective advantages are not always so apparent in the literature. There is indeed a growing interest in the daily life of patients including their management of physical and emotional pain, the perception of quality of life, and pulmonary function recovery. This review aims to highlight the advantages of minimal invasive surgery on pain, quality of life, and functional pulmonary recovery after lobectomy alone for early stage non-small cell lung cancer. Minimal invasive techniques or limited sparing open techniques offer better results in term of postoperative pain than open non-sparing techniques, allowing a lighter analgesia protocol. However, these clear benefits seem to disappear in the mid-term postoperative period. Studies suggest that minimal invasive surgery is non-inferior to thoracotomy in terms of quality of life, and seems to give patients at least a better vision of their health, but larger-scale studies are needed to demonstrate its superiority. Data show clear advantages in the postoperative pulmonary function recovery for minimal invasive surgery compared to that of open procedures, although sparing and anterior incisions can show equivalence. That benefit does not seem to persist in the mid and long term. Nevertheless, the posterolateral thoracotomy appears to have the worse effect on the loss of pulmonary function.

Keywords: Lobectomy, lung cancer, quality of life, pain, pulmonary function



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INTRODUCTION

Lobectomy for early stage non-small cell lung cancer has been described in the last decade with a large variety of approaches^[1]. Open surgery can be performed by an anterior, axillary, or posterolateral incision. Muscle-sparing techniques have recently been adopted to limit the thoracic trauma. The development of video-assisted thoracoscopic surgery (VATS) first enabled reducing the size of the thoracotomy, usually anterior, and is actually limited to the trocar incisions or a single portal approach. More recently, robotic assisted surgery (RATS) offers better ergonomics as well as three-dimensional imaging^[2,3]. Despite many papers encouraging clear benefits on pain for minimally invasive techniques, criticism must be made of the compared surgical open methods, mostly involving non-sparing techniques.

In this paper, we focus on pain, quality of life, and functional pulmonary recovery after lobectomy for early stage non-small cell lung cancer depending on the surgical technique. This represents an important aspect in the rise of patients' involvement in their own care^[4].

Relevant studies were obtained by searching the PubMed and Uptodate databases until 31 October 2019. The search terms included "lung cancer" AND "lobectomy" AND "pain" OR "quality of life" OR "pulmonary function" in the title, abstract, and keywords. Tables 1 and 2 summarize characteristics and operative details of the cited articles.

PAIN

Pain assessment is subjective and depends on the personal tolerance, culture, and psychological context. The postoperative analgesia protocol will influence the results. Pain is an important factor because it can result in hard coughing and mobilization, leading to potential secondary pneumonia. Pain management after surgery is obviously a basic principle in current medical care. Having pain at the surgery site for more than two months is considered as chronic pain.

Analgesia can be provided by epidural or para-spinal catheter placed before surgery; inter-costal nerve block, para-vertebral catheter, or wound infiltration during surgery; and patient-controlled/not controlled intravenous analgesics, intramuscular, oral, or suppository postoperatively. Catheter analgesics are usually stopped after removal of the thoracic drain.

The most used questionnaires for pain are the Visual Pain Score, the Visual Analog Scale, and the Numerical Rating Scale^[5]. In addition, chronic pain can be evaluated by the Pain Detected Questionnaire.

Several studies showed clear benefit on pain from minimal invasive techniques compared to non-sparing thoracotomies: a prospective study^[6] showed a significant decrease of the postoperative pain at Days 0, 1, 7, and 14 in a VATS group (two trocars with a 7-cm-long anterior incision) compared to a non-sparing posterolateral thoracotomy group (with one or two ribs resection and no muscle sparing). All patients had an epidural catheter. A similar retrospective study^[7] showed a significant decrease in the postoperative pain in a VATS procedure (6-cm anterior access incision and three trocars) compared to an anterolateral thoracotomy (12 cm long with a section of a costal cartilage but muscle sparing) at the first week after surgery. That difference disappeared in the second postoperative week. A continuous epidural analgesia was present for every patient until the third postoperative day.

A prospective randomized study^[8] compared VATS (with three-trocar technique and a 4-cm anterior utility incision) and anterolateral thoracotomy (16-cm incision) with muscle and rib sparing, every patient receiving an epidural catheter. They assessed the postoperative pain by Numerical Rating Scale at 2, 4, 8, 12, 26, and 52 weeks and found a significantly lower level of pain in the VATS group during the entire follow-

Table 1. Main characteristics of publications related to pain and respiratory recovery after lobectomy

First author	Published	Country	Subject	Period	n	Type	Comparison groups
Kwon <i>et al.</i> ^[11]	2017	USA	Pain (VPS and PDQ)	2010-2014	502	Retrospective	RATS <i>vs.</i> VATS <i>vs.</i> open
Van der Ploeg <i>et al.</i> ^[12]	2019	The Netherlands	Pain (NRS)	2015-2016	57	Retrospective	RATS <i>vs.</i> VATS <i>vs.</i> open
Nakata <i>et al.</i> ^[23]	2000	Japan	Respiratory function (arterial blood gaz, FVC, FEV1 and PFR)	Nov 1996-Aug 1997	21	Retrospective	VATS <i>vs.</i> open
Nomori <i>et al.</i> ^[24]	2003	Japan	Respiratory function (VC and 6MWT)	1991-2000	112	Retrospective	VATS <i>vs.</i> open
Nagahiro <i>et al.</i> ^[6]	2001	Japan	Pain (VAS) and respiratory function (VC, FVC and 6MWT)	Jun 1999-Apr 2000	22	Prospective non randomized	VATS <i>vs.</i> open
Handy <i>et al.</i> ^[10]	2009	USA	Pain (VAS), QOL (SF36) and respiratory function (FEV1 and 6MWT)	1998-2007	241	Retrospective	VATS <i>vs.</i> open
Bendixen <i>et al.</i> ^[8]	2016	Denmark	Pain (NRS) and QOL (EQ5D and EORTC QLQ-C30)	Oct 2008-Aug 2014	206	Prospective randomized	VATS <i>vs.</i> open
Nomori <i>et al.</i> ^[7]	2001	Japan	Pain (VAS) and respiratory function (VC, 6MWT and respiratory muscle strength)	Aug 1999-Dec 2000	66	Retrospective	VATS <i>vs.</i> open
Andreetti <i>et al.</i> ^[9]	2014	Italy	Pain (VAS)	Apr 2011-Jan 2013	145	Prospective non randomized	VATS <i>vs.</i> open

VPS: visual pain score; PDQ: pain detected questionnaire; NRS: numerical rating scale; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 sec; PFR: peak flow rate; 6MWT: 6 min walking test; VAS: visual analog scale; EQ5D: euroQol 5 dimensions; EORTC QLQ-C30: european organisation for research and treatment of cancer 30 item quality of life questionnaire

up. A comparable prospective study^[9] evaluated pain by Visual Analog Scale at 1, 12, 24, and 48 h between VATS (three-trocar technique and an anterior access incision of 4 cm) and anterolateral thoracotomy (a 9-10-cm incision) with muscle and rib sparing, showing a significantly lower level of pain for VATS. All patients benefited from an intercostal nerve block and continuous intra-venous analgesia.

Mid-term evaluation has been reported^[10] with no significant difference in the pain level (using Visual Analog Scale) at six months between open procedures (thoracotomy with muscle sparing or median sternotomy) and VATS (a three-trocar technique with an anterior 5-6-cm incision). Although the pain level was the same, there was a significantly lower consumption of painkillers in the VATS group.

An interesting retrospective study^[11] compared RATS, VATS, and posterolateral thoracotomy (PLT) in terms of pain from the first to the ninth postoperative day (by Visual Pain Score) and at two months (by Pain Detected Questionnaire). The RATS consisted in a 4 + 1-port technique while the VATS was a three- or four-port technique, with an access incision less than 5 cm long. The PLT was mostly serratus sparing with resection of the sixth rib. Thoracotomies benefited from epidural or para-spinous catheter while minimal invasive surgery (MIS) had intercostal nerve block and PCA. The study showed no significant difference for acute or chronic pain between VATS and RATS, but a significant difference between MIS and thoracotomy starting at Postoperative Day 4. Concerning the chronic pain, no significant difference was noticed between MIS and thoracotomy.

A similar study^[12] also evaluated minimally invasive approaches (VATS and RATS) and anterolateral thoracotomy (ALT) at Postoperative Day 1, 3, and 5 via Numerical Rating Scale. All patients benefited from thoracic epidural analgesia. The RATS used 4 + 1 ports, the VATS three trocars with a 4-cm anterior utility incision, and the anterolateral thoracotomy was 20 cm long with muscle sparing but no rib resection. There

Table 2. Comparative technical details of publications related to pain and respiratory recovery after lobectomy

Ref.	n				Description	Open	Pain	QOL	Respiratory function
	RATS	VATS	Open	RATS					
Kwon <i>et al.</i> ^[11]	74	227	201	4 + 1 ports	3 or 4 ports, access incision less than 5 cm	PLT generally muscle sparing, resection of the sixth rib	MIS > open for acute pain ($P = 0.0004$) MIS = open for chronic pain ($P = 0.1966$)		
Van der Ploeg <i>et al.</i> ^[12]	22	17	18	4 + 1 ports	3 ports, 4 cm anterior access incision	ALT of 20 cm long with muscle sparing and no rib resection	MIS = open at POD 1, 3 and 5 ($P = 0.51$; 0.07; 0.26)	VATS > open for PFR ($P = 0.008$ and 0.03 at POD 7 and 14)	
Nakata <i>et al.</i> ^[23]	10	11		2 ports, 6-10 cm anterior access incision	PLT division of the muscles and two ribs		VATS = open for PaO ₂ ($P = 0.054$), SaO ₂ ($P = 0.063$), FVC ($P = 0.1$), FEV1 ($P = 0.08$)	VATS > open for PFR ($P = 0.008$ and 0.03 at POD 7 and 14) VATS = open for PaO ₂ ($P = 0.054$), SaO ₂ ($P = 0.063$), FVC ($P = 0.1$), FEV1 ($P = 0.08$)	
Nomori <i>et al.</i> ^[24]	28	28 × 3		3 trocars, 5-6 cm axillary access incision	Muscles and one or two costal cartilages divided		PLT < ALT/AAT/VATS for VC ($P < 0.05$) and 6MWT ($P < 0.01$) AAT < ALT/VATS for 6MWT ($P < 0.05$, $P < 0.001$)	VATS > PLT for FVC ($P = 0.011$), for FEV1 ($P = 0.039$) and VC ($P = 0.019$)	VATS = open for FEV1 ($P = 0.17$) and 6MWT ($P = 0.14$)
Nagahiro <i>et al.</i> ^[6]	13	9		2 ports, 7 cm anterior incision	ALT 12 cm AAT 20-25 cm PLT 30-35 cm	VATS > PLT at POD 0, 1, 7, 14 ($P < 0.05$)	Post op VATS > open for pain and general health ($P < 0.05$) Post op open < VATS for physical functioning, role and social functioning ($P < 0.05$)	VATS > PLT for FVC ($P = 0.011$), for FEV1 ($P = 0.039$) and VC ($P = 0.019$)	VATS = open for FEV1 ($P = 0.17$) and 6MWT ($P = 0.14$)
Handy <i>et al.</i> ^[10]	49	192 (64 TH and 128 MS)		3 ports, 5-6 cm anterior incision	TH with muscle sparing MS	VATS = open ($P = 0.08$)	Post op VATS > open for pain and general health ($P < 0.05$) Post op open < VATS for physical functioning, role and social functioning ($P < 0.05$)	VATS > open for FEV1 ($P = 0.014$)	VATS = open for FEV1 ($P = 0.17$) and 6MWT ($P = 0.14$)
Bendixen <i>et al.</i> ^[8]	103	103		3 ports, 4 cm anterior incision	ALT of 16 cm incision with muscle and rib sparing	VATS > open for moderate to severe pain ($P < 0.0001$)	VATS = open for EQ5D ($P = 0.014$) VATS = open for QOLQ-C30 ($P = 0.13$)		
Nomori <i>et al.</i> ^[7]	33	33		3 trocars, 6 cm anterior incision	ALT of 12 cm long with section of a costal cartilage but muscle sparing	VATS > ALT the first week ($P < 0.05$) VATS = ALT the second week ($P = 0.09$)		VATS > ALT at one week for respiratory muscle strength ($P = 0.07$) and 6MWT ($P = 0.06$)	
Andreotti <i>et al.</i> ^[9]	75	70		3 trocars, anterior incision of 4 cm	ALT of 9-10 cm with muscle and rib sparing	VATS > ALT ($P = 0.000$)		VATS > ALT for FEV1 ($P = 0.028$) and 6MWT ($P = 0.000$)	

PLT: postero-lateral thoracotomy; MIS: minimally invasive surgery; POD: post operative day; PFR: peak flow rate; ALT: anterior limited thoracotomy; AAT: anteroaxillary thoracotomy; 6MWT: 6 min walking test; FEV1: forced expiratory volume in 1 second; EQ5D: euroQol 5 dimensions; QOLQ-C30: 30 item quality of life questionnaire; VATS: video-assisted thoracoscopic surgery; RATS: robotic assisted surgery; VC: vital capacity; MS: median sternotomy; TH: thoracotomy; QOL: quality of life

were no significant differences on pain among the surgical techniques; a non-significant benefit for RATS was noticed.

The technical details for the RATS and VATS procedures are quite similar considering the number of ports (2-4 for VATS and 4 + 1 for RATS) and the length of the access incision (4-7 cm). The number of ports does not seem to impact the postoperative pain^[13]. However, thoracotomy techniques greatly vary, with anterior or posterior incisions, and muscle/rib sparing or non-sparing techniques. Non-randomized studies usually indicated small and peripheral tumors for MIS, while open procedures were performed for larger and central tumors.

We can conclude that, in the early postoperative period, minimal invasive techniques or limited sparing open techniques offer better results with respect to pain compared to large and non-sparing open techniques. The MIS techniques allow a lighter analgesia protocol. However, the clear benefits on pain from the MIS seem to disappear in the mid-term postoperative period.

QUALITY OF LIFE

Quality of life is defined by the World Health Organization as “individual’s perceptions of their position in life in the context of their culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”^[14]. We focus here on how daily life is impacted by the surgery.

Two questionnaires are mainly used for this assessment: the Short Form 36 Health Survey (SF36) and the European Organization for Research and Treatment of Cancer 30-Items Quality Of Life Questionnaire (EORTC QLQ C30)^[15-18]. The first one evaluates patients on both physical and emotional component scales that can be compared to the healthy population. The second one is more focused on the cancer population and evaluates the impact of the disease and its treatment on the daily life.

A prospective study^[19] described a one-month temporary decrease in quality of life (QOL) functioning scores (EORTC QLQ C30) after lobectomy, with concomitant increase in pain and dyspnea. The scores return to baseline at three months postoperatively. Comparing thoracotomy to VATS, significant differences are seen in favor of VATS in this study. Antero- and posterolateral thoracotomy are comparable for QOL evolution.

However, while improvements in QOL have been demonstrated in a few studies in favor of MIS, there is no current evidence supporting its superiority. A retrospective study^[9] compared the quality of life between VATS and open procedures (median sternotomy and muscle sparing thoracotomies) preoperatively and at six months after the surgery using the SF36 questionnaire. It showed no significant difference at 6 months. However, in the VATS group, a significant improvement at 6 months is described for bodily pain and general health compared to the preoperative status. Regarding the open group, a significant worsening is highlighted after the surgery on the physical functioning, role, and social functioning.

A prospective study^[20] using SF36 every four months after surgery for 12 months showed similar physical component summary between VATS and thoracotomy during the first 12 months after surgery, with a mental component summary score worse in the VATS group at four and eight months. Such results might be explained by the higher expectations by the patients for MIS.

A quite exhaustive protocol study^[8] evaluated two questionnaires [EuroQol 5 Dimensions (EQ5D) and EORTC QLQ C30] at 2, 4, 8, 12, 26, and 52 weeks after surgery (VATS and anterolateral thoracotomy). EQ5D questionnaire evaluated mobility, self-care, usual activities, pain and discomfort, anxiety, and depression. The scores for EQ5D were significantly better during the entire follow up for the VATS group while there was no significant difference for the EORTC QLQ C30 between VATS and open surgery. The

emotional function was the only subgroup where VATS was significantly better than open in the EORTC QLQ C30.

Robotic surgery was evaluated with the SF-12 questionnaire at three weeks and four months in a propensity-matched analysis^[21] considering rib and nerve sparing thoracotomies. Patients reported better QOL scores in the RATS group. In particular, a higher mental QOL score three weeks postoperatively was noticed. A similar trend was observed for physical QOL without statistical significance. At four months, there was no difference between the two groups.

The major difficulty concerning QOL assessment is the important interaction between pain and respiratory function. In conclusion, studies suggest that MIS is non-inferior to thoracotomy in terms of QOL, and seem to give patients at least a better vision of their health, but larger-scale studies are needed to demonstrate its superiority.

RESPIRATORY FUNCTION RECOVERY

Pulmonary function is objectively evaluated in the postoperative period by the Vital Capacity (VC) or Forced Vital Capacity (FVC) and the Forced Expiratory Volume in one second (FEV₁). A more practical evaluation can also be performed with the 6 Minutes Walking Test (6MWT)^[22]. The preoperative pulmonary function is mandatory to measure its evolution postoperatively. One must keep in mind that patients who undergo VATS are often selected because they have worse preoperative conditions.

Studies evaluating VATS and non-sparing thoracotomies clearly show superiority for MIS. VATS and PLT^[23] were compared in terms of arterial blood gas analyses (PaO₂ and PaCO₂) at 4, 7, and 14 days after surgery and the pulmonary function (FVC, FEV₁, and Peak Flow Rate) at 7 and 14 days, as well as at one year. The VATS consisted in a 6-10-cm anterior access incision with two trocars while the PLT divided the muscles and two ribs. Only patients from the PLT group benefitted from a continuous epidural anesthesia. They observed no significant difference concerning the arterial blood gas analyses between the two groups. Pulmonary testing was significantly better for VATS at Days 7 and 14. There was no difference at one year between the two groups. Another study also demonstrated significant benefit for VATS^[6] when comparing VC, FVC, and FEV₁ at one and two weeks postoperative between VATS and posterolateral thoracotomy with muscle division and one rib resection.

VATS and various thoracotomy approaches were compared with the VC parameter measured at 1, 2, 4, 12, and 24 weeks after surgery, and the 6MWT at one week^[24]. They performed VATS with a 5-6-cm axillary incision and three trocars, while the thoracotomies always divided the concerned muscles and one or two costal cartilages (anterolateral, axillary, and posterolateral approach). The lengths of the incisions were, respectively, 12, 20-25, and 30-35 cm. All patients benefited from a continuous epidural analgesia. They also noted a clear significant disadvantage in the posterolateral group regarding VC and 6MWT. VATS, anterolateral, and axillary approaches were not different in terms of VC during the follow-up while the 6MWT was significantly better in the VATS and anterolateral groups compared to axillary and posterolateral groups.

Equivalent results for VATS and anterolateral thoracotomy approaches have been confirmed^[7] with no difference in term of VC, 6MWT, and respiratory muscle strength (measured with the maximal expiratory and inspiratory pressure)^[25] at one and two weeks after VATS or anterolateral thoracotomy. However, other studies have demonstrated the opposite^[9] with a significant advantage of VATS in comparison with anterolateral, muscle sparing thoracotomy, concerning FEV₁ and 6MWT at two days and one month after surgery.

The mid-term impact has been studied^[10] using FEV1 and 6MWT at six months of VATS and open procedures, being thoracotomy or sternotomy. No significant difference has been demonstrated.

These data show advantages in the postoperative pulmonary function recovery for MIS compared to open procedures, although sparing and anterior incisions can show equivalence. That benefit does not seem to persist in the mid and long term. Nevertheless, the posterolateral thoracotomy appears to have the worse effect on the loss of pulmonary function.

CONCLUSION

We are now evolving to the era of minimal invasive surgery, not only for esthetic reasons but mainly to reduce the surgical stress of the procedures on our patients. There is scientific evidence for equivalent oncological control by minimal invasive as by open surgery^[26].

Through this review of the literature, we can assume that such equivalence seems evident concerning postoperative pain, quality of life, and respiratory function recovery, and the superiority of minimal invasive surgery may be assumed for the early postoperative period. These parameters are indeed quite subjective and interact with each other. Their evaluation needs compliance from the patients in the long run. Nowadays, smartphone applications may be a solution to improve follow-up.

DECLARATIONS

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Wrote and reviewed: Goussens A, Lacroix V

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Transcatheter mitral valve implantation: different fixation techniques

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Abstract

Transcatheter mitral valve implantation provides an off-pump treatment option for mitral valve regurgitation, especially for secondary mitral regurgitation. It offers an opportunity for the treatment of a large cohort of patients not referred for conventional surgery. One of the biggest challenges is the development of a valved stent that suits the complex anatomy of the native mitral valve. Furthermore, secure anchorage of the device is difficult in the mitral area without clearly defined structures. In the last few years, various new self-expanding nitinol valved stents for transapical implantation in the beating heart have been developed. Different design iterations were conducted to improve fixation and overall stent performance. The risk of paravalvular leakage was decreased and reproducibility enhanced. This article reviews the major achievements in the development process of our apically fixed mitral valved stent over the last few years, with prototypes that provide secure stent deployment, high reproducibility and low paravalvular leakage rates.

Keywords: Mitral valve, transcatheter, valved stent, off-pump, fixation techniques

INTRODUCTION

The development of transcatheter mitral valve implantation is the focus of recent research. This novel procedure provides a means to treat severe and symptomatic mitral insufficiency, especially secondary mitral regurgitation, without the need for ECMO during surgery. The transcatheter mitral valve implantation device includes heart valved stents that are implanted into the beating heart using a transcatheter-guided technique. This novel technology is ideal, especially for older patients, who are classified as high-risk patients or not



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operable. Due to the advanced age and severe comorbidities, approximately 49% of patients suffering from severe and symptomatic mitral valve insufficiency are not candidates for open-heart surgery^[1].

Challenges in the development process of such mitral valved stents include: high pressure within the left heart chamber, secure fixation to the complex anatomy of the mitral valve apparatus, absence of left ventricular outflow tract obstruction, and a tight seal to prevent the occurrence of paravalvular leakage after valved stent implantation. Due to very high pressures within the left ventricle, which act on the closed mitral valve, the development of strong systolic fixation of the device to prevent migration into the left atrium is of particular importance during the research and developmental process.

TETHERED APICAL FIXATION (LUTTER VALVE)

The first implantations of an apically tethered transcatheter mitral valve were reported in five studies between 2008 and 2013. The device was made of a self-expanding nitinol stent with a tubular ventricular part and an atrial cuff. The stent was covered with a polytetrafluoroethylene membrane and carried a trileaflet bovine pericardial valve [Figure 1]. In total, 36 pigs received off-pump mitral valved stent implantation with this device. Seventeen pigs were followed up for 1 h after implantation^[2-4], one animal for 6 h, four animals for 1 week^[5], five animals for 1 month, four animals for 2 months and one animal for 3 months^[6,7]. Six animals died during the surgery or within the first hours after implantation: two suffered from ventricular fibrillation, two died from prosthesis mispositioning and two from incorrect fixation.

Transesophageal echocardiography (TEE) and computed tomography (CT) were used to evaluate stent function and correct positioning. Seven of 32 animals showed mild regurgitation after mitral valved stent implantation and a few stent fractures were observed after post-mortem valve explantation. Nevertheless, no valve stent migration, embolization, systolic anterior movement or left ventricular outflow tract obstruction was observed in the surviving animals. Gross evaluation revealed tissue coverage of the atrial element of the stent after four to eight weeks and the new, apically-tethered mitral valved stent showed good overall valve function in all cases after two and three months. These first studies demonstrated the feasibility of a reproducible method of deployment of the mitral valved stent with low gradients across the left ventricular outflow tract, and adequate stent function for up to three months in a large animal model.

COMPUTED TOMOGRAPHIC EVALUATION OF DIFFERENT PROTOTYPE DESIGNS

The *in vivo* shaping of mitral valved stent prototypes composed of a tubular ventricular body connected to an atrial element at different angles (45°, 90°, 110°) was evaluated using CT in 11 pigs^[8]. CT was successfully carried out 3 weeks after implantation and stent shaping, as well as left ventricular outflow tract obstruction, was controlled [Figure 2] and stent position was correct in all animals. Nevertheless, stent body deformations at the atrio-ventricular junction were detected in all cases, with the biggest deflection of the prototypes at an angle of 45°. A larger preset angle demonstrated less deflection and improved the alignment, thus reducing the mechanical load on the stent. Obstruction of the outflow tract was observed in two animals^[8].

APICAL FIXATION FORCES

To estimate the quantification of apical fixation forces of a tethered mitral valved stent, a study was carried out by Pokorny et al.^[9]. With a specifically designed test setup, the forces acting on the apical fixation tethers were successfully measured in 18 animals [Figure 3]. The apical fixation forces were recorded following off-pump mitral valved stent implantation. In this study, two different stent designs were used. The first group ($n = 10$) had a sole apical fixation and the second ($n = 8$) had additional sub-annular fixation. The mean fixation forces were higher in the former and a significant reduction of the force acting on the apex was achieved with the latter^[9].

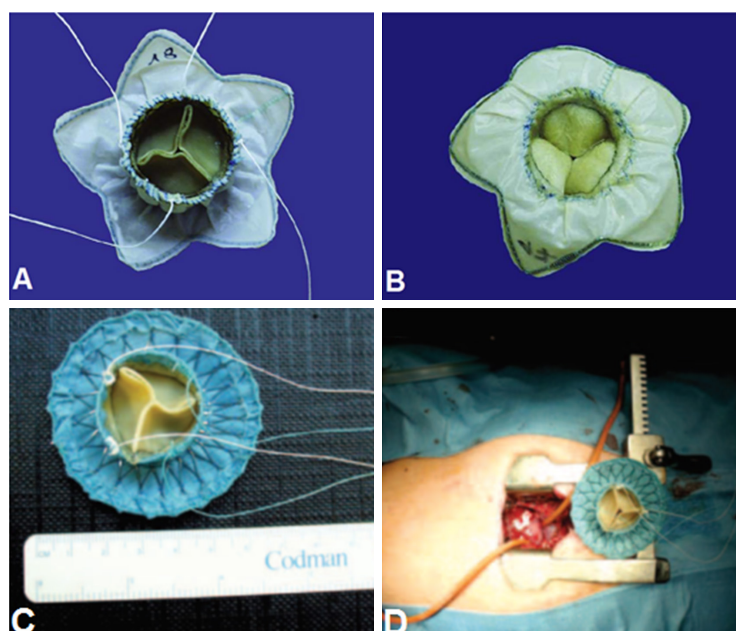


Figure 1. A: ventricular view of the atrioventricular valved stent. It consists of a bovine pericardial valve of 27 mm diameter, a custom-made nitinol stent, and a ventricular fixation system consisting of the annular radial force of the nitinol stent and four tethers fixed at the apex; B: atrial view of the prototype valved stent^[3]; C: ventricular view of the new refined mitral valved stent; D: operative setting after ministernotomy (2 inches) with this valved stent and apex of the heart with purse-string sutures is exposed^[6]

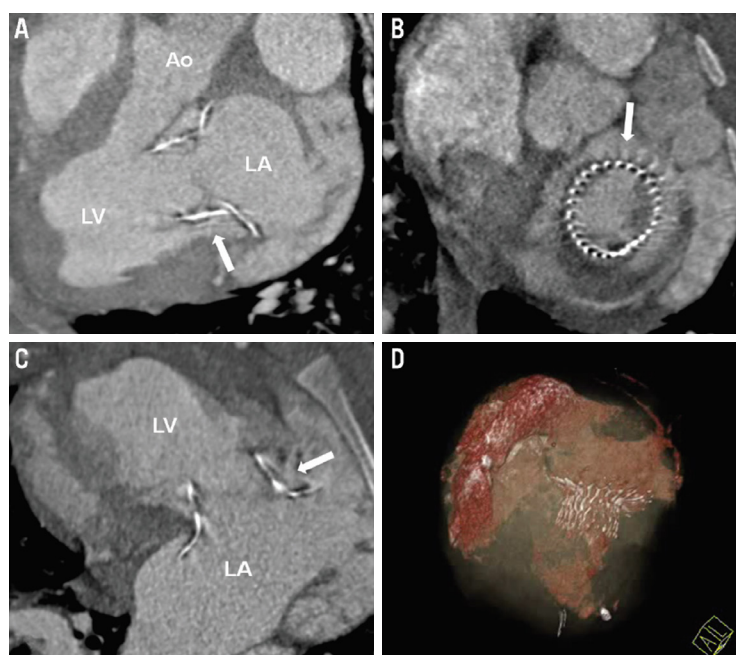


Figure 2. A-C: cardiac CT short- and long-axis standard views showing correct stent position and no left ventricular outflow tract obstruction of the 110° prototype 1 month after implantation; D: three-dimensional reconstruction showing the nitinol stent frame and left atrial and ventricular volumes. Reprinted from *EuroIntervention*, Pokorny et al.^[8], Transapical mitral valved stent implantation: computed tomographic evaluation of different prototype designs, 948-955. Copyright (2015), with permission from Europa Digital & Publishing. Ao: aorta; LA: left atrium; LV: left ventricle (white arrow indicates the nitinol stent frame)

SUB-ANNULAR FIXATION

A mitral valved stent with apical and additional sub-annular fixation was presented in a study in 2016 [Figure 4]^[10]. Ten pigs received off-pump mitral valved stent implantation of this novel design. Acute TEE

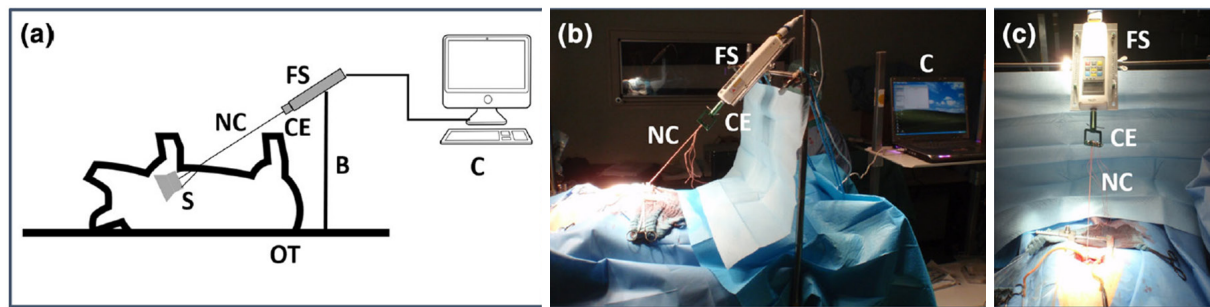


Figure 3. Illustration of the force measurement system developed: (a) schematic diagram of the test set-up; (b) lateral view of the test set-up during force quantification after mitral valve stent implantation; (c) frontal view of the FS connected to the NC via the CE. S: stent; NC: neo-chords; FS: force sensor; CE: connecting element; B: fixation bridge; C: computer for digital data recording^[10]

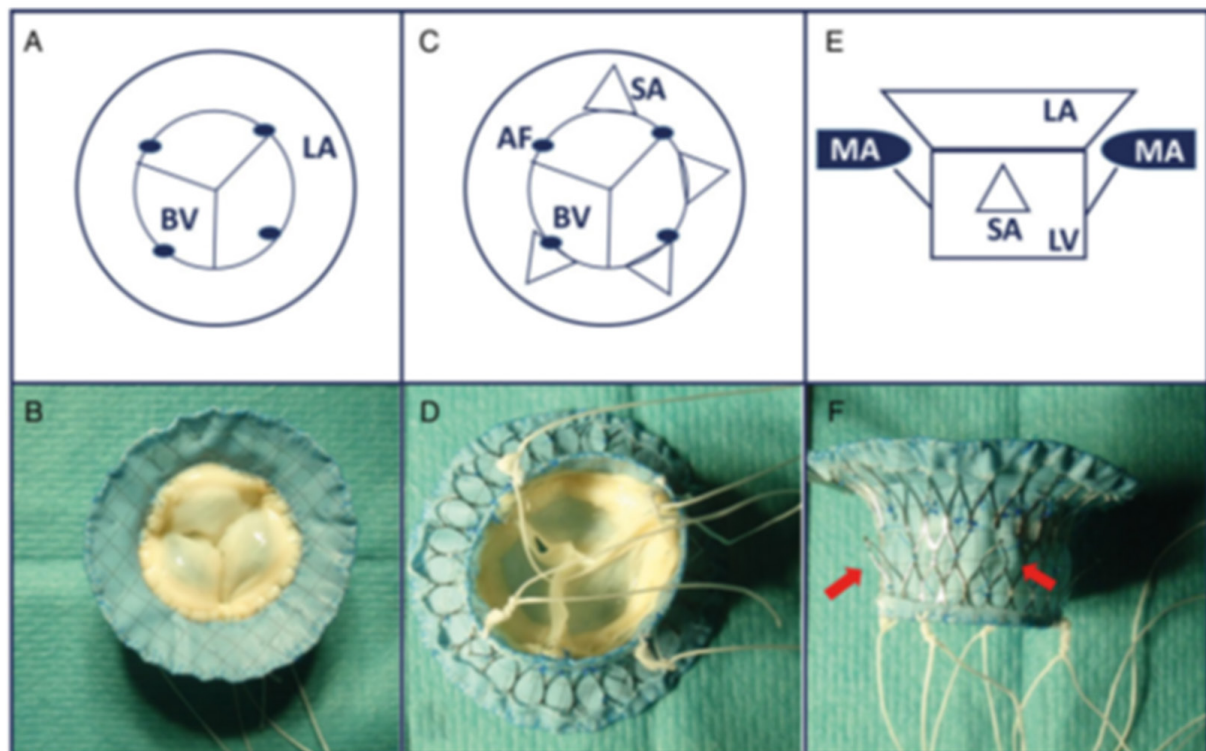


Figure 4. Illustration of the mitral valve stent prototypes with apical and additional sub-annular fixation elements (red arrows), comprising atrial element (LA), ventricular body (LV) and BV. The AF points are indicated by dots. A and B: apical view; C and D: ventricular view of the prototype SA with additional subannular fixation; E and F: lateral view of the prototype SA12. LA: left atrium; LV: left ventricle; BV: bioprosthesis heart valve; AF: apical fixation; MA: mitral annulus; SA: sub-annular

and haemodynamic evaluations were assessed 60 min post implantation. Haemodynamic stability, low gradients and physiological longitudinal function were achieved. In nine cases, paravalvular leakage was trace or less. Furthermore, decreased ejection fraction, several stent fractures and an overall lower survival time compared to sole apical fixation were observed with this fixation method^[11].

SUPRA-ANNULAR FIXATION

Special small fixation hooks were developed and fabricated and a supra-annular fixation method was established. These hooks were mounted on the atrial part of the mitral stent to penetrate into the surrounding annular tissue to serve as an additional fixation [Figure 5A and B]^[10]. In an *in vivo* study

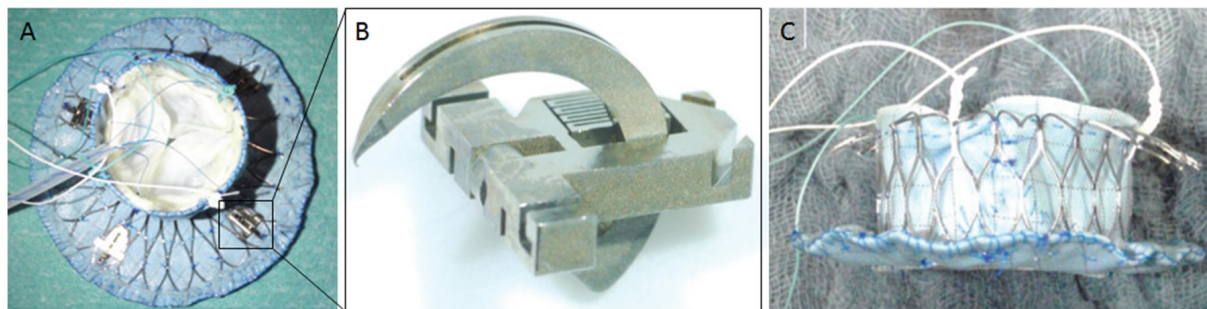


Figure 5. A: mitral valve stent with apical and additional supra-annular fixation elements; B: hook shaped elements; C: mitral valve stent with apical and subsequent sub-valvular fixation rim^[13]

with five pigs, stents were equipped with three ($n = 2$) or four hooks ($n = 3$) as well as four neo-chords for apical fixation and implanted in an off-pump procedure. A thread system enabled successful deployment of the hooks within the heart in four of five cases. One animal died within hours after implantation due to a prosthesis mismatch; one animal was sacrificed after two weeks; three animals were followed up to 1 month; and one animal was followed to three months with excellent health. Good valve function as well as normal left ventricular function was demonstrated by TEE and haemodynamic evaluation^[11].

SUB-VALVULAR FIXATION

A modified nitinol valved stent with a ventricular rim was developed for sub-valvular fixation [Figure 5C]. For secure fixation, an additional apical fixation system was attached to these stents^[11]. This prototype was successfully implanted in an off-pump procedure in ten animals. A higher degree of ventricular fibrillation occurred in this group. In four of ten cases, multiple areas of infarction, arrhythmia and in one case, persistent atrial fibrillation was observed after valved stent implantation. Eight animals died within the first day of implantation. The other two animals were weaned from anaesthesia and followed up for a period of two and seven days. Nevertheless, a reduction in left ventricular ejection fraction compared to baseline values was also observed in this study group.

CONCLUSION

The correct positioning and sufficient fixation of a transcatheter mitral valve stent is a challenging task and the topic of several studies and developments in recent years. Our group specializes in the development of apical fixation methods and its *in vivo* evaluation. Different fixation techniques such as sole apical fixation and a combination of apical fixation with sub-annular, supra-annular or sub-valvular fixation have been presented in this review.

Even though sole apical fixation showed promising results in animal studies and already has very good results in clinical studies with the Tendyne mitral valve prosthesis in more than 150 patients (mainly in the USA and Australia), fixation force measurements demonstrated the advantage of a combined fixation strategy. In the meantime, the latter received the CE mark in March 2020. Though transseptal implantation of the mitral valve stent through the femoral access site is less invasive and expected, transapical left ventricular implantation is, at the moment, the only route to deliver the whole material to the mitral annulus and allow additional secure fixation. Perhaps smaller valve prostheses and newer fixation techniques will allow transfemoral access in the future. Consequently, different combinations of fixation concepts are continuously under development in large animal and pre-clinical studies. To succeed, *in vivo* quantification of mechanical deformations of the stent by CT should be performed after implantation to identify critical areas in stent design. Finally, the alignment and reduction of mechanical stress on the stent frame should be topics for further stent frame development.

DECLARATIONS

Authors' contributions

Wrote the manuscript and invented the stent prosthesis: Lutter G

Drafted the manuscript and substantially revised it: Frank D, Hansen JH, Cremer J

Contributed to the conception and design of the studies and performed data analysis and interpretation of the data, they drafted the manuscript and substantially revised it: Liu Y, Haneya A, Puehler T

Availability of data and materials

Not applicable.

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Conflicts of interest

Prof. Georg Lutter and Prof. Derk Frank: consultants to Abbott, Edwards and Medtronic. All other authors have nothing to disclose.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Robotic thymectomy for myasthenia gravis

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Abstract

Thymectomy is an effective treatment option for the management of myasthenia gravis, as demonstrated by a recent multicenter randomized clinical trial. Complete removal of all thymic tissue, including ectopic foci, increases the chance of achieving a remission or a substantial improvement of the disease; therefore, extended transsternal thymectomy was long considered the procedure of choice. Over the years, several minimally invasive approaches have been proposed, with the aim to reduce perioperative morbidity and to improve aesthetics; however, concerns exist that through such approaches, it may not be possible to achieve a complete resection. Robotic thymectomy seems to overcome many of the limitations associated with other minimally invasive approaches. The available evidence suggests that robotic thymectomy for myasthenia gravis is a safe procedure, and that long-term neurological outcomes are satisfactory.

Keywords: Thymectomy, robot, myasthenia gravis

INTRODUCTION

Myasthenia gravis (MG) is a neuromuscular disease that manifests with fluctuating and fatigable weakness of different muscle groups. It occurs because of the production of autoantibodies directed against the components of the neuromuscular junction^[1]. The medical management of MG includes the use of symptomatic therapy (anticholinesterase) and immunosuppressive treatment.



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Blalock and colleagues^[2], in 1939, were the first to report a dramatic improvement in symptoms following thymectomy in a patient affected by a cystic thymic tumor and MG. Since then, several other reports followed, highlighting a positive outcome of thymectomy in nonthymomatous MG^[3]. However, in the absence of any formal evidence, the real benefit of this procedure remains in doubt.

Retrospective studies were analyzed by an in-depth review in 2000^[4]; while the majority of reports demonstrated a favorable response from thymectomy in rates of disease remission or improvement, several methodological flaws precluded the investigators from drawing firm conclusions. A major breakthrough in the role of thymectomy for nonthymomatous MG was made only recently in 2016 by the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX)^[5]. This large international, randomized, single-blind trial was conducted to determine whether extended transsternal thymectomy combined with a standardized prednisone protocol would be superior to prednisone alone after 3 years. A total of 126 patients from 36 institutions affected by generalized nonthymomatous MG, with strict inclusion criteria (age of 18 to 65 years, Myasthenia Gravis Foundation of America (MGFA) clinical class II to IV disease, positivity for acetylcholine-receptor (AChR) antibody, and disease duration less than 5 years) were randomized into the two treatment arms. The results from this study unequivocally demonstrated that thymectomy was beneficial with respect to clinical outcomes and requirements for prednisone therapy in patients affected by generalized nonthymomatous MG^[6].

Over the years, surgical approaches to thymectomy have evolved, with the aim of reducing surgical morbidity and of increasing the acceptance of such procedure for benign diseases, especially in young patients. Minimally invasive approaches include transcervical, videothoracoscopic (VATS), subxyphoid, and robot-assisted (RATS; robot-assisted thoracic surgery) thymectomy^[7]. Various authors and meta-analyses have demonstrated that minimally invasive approaches to thymectomy are associated with better surgical outcomes and fewer surgical complications than the transsternal open approach, with no significant differences in MG complete remission rates^[8].

Currently, there is no definitive evidence in the literature that supports the use of one minimally invasive approach over the others; therefore, the decision is mostly based on the surgeon's preference. Factors that play a role in the choice of the surgical approach are perceived difficulty, ergonomics and the learning curve of the procedure, as well as the possibility of carrying out a thorough, extended thymectomy, which means the removal of the whole thymus with the surrounding fatty tissue of the neck and the mediastinum^[9]. This is a capital concept in surgery for MG, as various authors have demonstrated that ectopic thymic foci are interspersed in the anterior mediastinal fat in up to 98% of patients, and that the removal of all thymic foci increases the probability of a complete remission of MG after surgery^[10,11].

At the Division of Thoracic Surgery of Padua University Hospital (Italy), starting from 2002, we developed a program of RATS thymectomy, and we currently adopt this approach for all patients who undergo thymectomy for nonthymomatous MG^[12]. In this article, the rationale, indications, technique and outcomes of robotic thymectomy for MG are reviewed.

RATIONALE FOR ROBOTIC THYMECTOMY

The most widespread robotic system nowadays is the Da Vinci surgical system (Intuitive Surgical, Inc. Sunnyvale, CA, USA). This consists of a designed surgeon's console, a vision system, and a patient-side cart supporting the interactive robotic arms. The console is connected to the video system and the robotic cart, and it represents the interface between the surgeon and the robotic system. The surgeon sees the operative field through binoculars located in the upper part of the console and his/her fingers grasp the master controls below the display and moves the robotic arms. The system translates the three-dimensional

movement of the hands and fingers into precise, identical, and real-time movements of surgical instruments inside the patient's chest.

Robotic thymectomy might be considered an evolution of the VATS approach. In fact, the high-resolution three-dimensional view of the operating field, attenuation of hand tremor and articulation of the robotic arms represent clear advantages of RATS over VATS thymectomy, especially in difficult to reach or narrow anatomical regions, such as the mediastinum. In the few studies where the RATS approach was compared with VATS, the investigators pointed out that the former approach is feasible and safe, and that it presents surgical advantages over the latter^[13,14]. Moreover, Rückert *et al.*^[13] noted an improved outcome in myasthenic patients operated on by a robotic approach compared with those operated by VATS, which could have been due to the superior mediastinal dissection achieved with RATS. On the other hand, RATS thymectomy has some disadvantages. First, it is more expensive than VATS thymectomy, with most of the expense being due to the acquisition of the robotic system, its annual maintenance and the disposable materials. Second, there is a lack of tactile feedback that could increase the risk of damaging delicate anatomical structures. However, this seems to be widely compensated by the superior three-dimensional view provided by the robotic console and the improved dexterity of robotic arms. Lastly, the operating surgeon is unscrubbed and placed away from the patient; therefore, in case of intraoperative complications requiring emergency conversion to sternotomy, another surgeon needs to stay sterile next to the patient^[15-17].

PATIENT SELECTION AND PREOPERATIVE PREPARATION

On the basis of current evidence, thymectomy is indicated for patients affected by generalized MG (grades II to IV, according to MGFA classification) and who are AChR antibody positive. No age limit exists; however, because it is an invasive procedure, the benefits of thymectomy have to be weighed against the risks of surgery, particularly in elderly patients. The chance of a complete remission of the disease decreases with age and with time from the onset of symptoms; therefore, there is general consensus that thymectomy should be offered early in the course of the disease of patients affected by MG^[6]. Thymectomy may be offered also to MG patients without detectable levels of AChR antibodies; however, current guidelines do not support thymectomy in patients with MuSK, LRP4, or agrin antibodies^[18]. Because of the long delay in onset of effect, thymectomy for MG is an elective operation; therefore, it should be proposed only to patients who are stable and deemed safe to undergo a procedure where postoperative pain and mechanical factors can limit respiratory function. In patients with thymomatous MG, surgery is indicated in any case to remove the tumor, regardless of the expected improvement in MG symptoms.

Preoperative workup includes contrast-enhanced computed tomography (CT), pulmonary function tests and blood gas analysis. The neurologist should evaluate all symptomatic patients to determine the need for intravenous immunoglobulin therapy or plasmapheresis in the immediate preoperative period.

SURGICAL TECHNIQUE

The surgical steps of robotic thymectomy are well described and there are only slight modifications in them across centers, as described elsewhere^[19]. Both a right-sided and a left-sided approach are feasible, and, while every surgeon has a preferred approach (at our center this is the left-sided one), the procedure should be tailored on the patient's anatomy, and there should be no hesitation to add a contralateral incision if required. The main goal, in fact, should be to achieve a radical en-bloc resection of all thymic tissue, from one phrenic nerve to another, and from the inferior poles of thyroid gland to the diaphragm. Advantages of the left-sided approach include a usually larger distribution of the thymic gland and of the mediastinal fat to the left side and around the left phrenic nerve, accessibility to the aortopulmonary window, and a better visualization of the contralateral phrenic nerve, which is protected in its superior portion by the superior

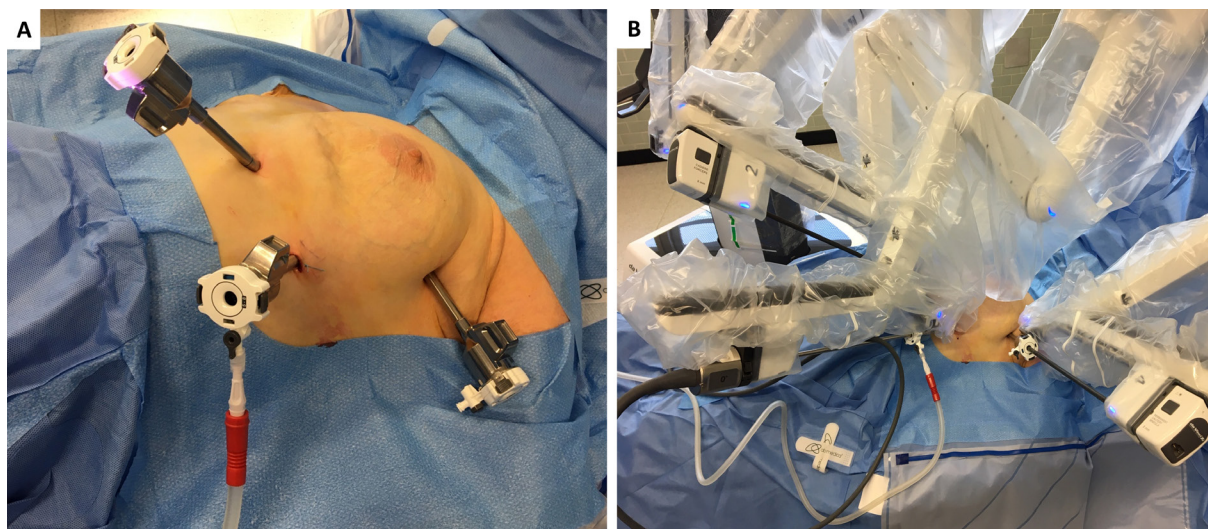


Figure 1. Port positioning and operative setup. A: the patient is positioned and draped. Ports are introduced on the fifth intercostal space on the midaxillary line, fifth intercostal space on the midclavicular line, and third intercostal space on the midaxillary line; B: the left arm is equipped with a grasping instrument (EndoWrist, Intuitive Surgical, Inc.), while the right arm has an Endo-dissector device (Intuitive Surgical, Inc.) with electric cautery function

vena cava. On the other hand, surgeons who prefer the right-sided approach like the larger space and the anatomical landmarks of the venous confluence.

The patient is under general anesthesia and single-lung ventilation. The operative side of the hemithorax is lifted 30° from the supine position with the aid of a bean bag inserted under the patient's back. The field is prepared and draped for a conversion to median sternotomy or for addition of another port on the contralateral side [Figure 1A]. The procedure begins with insertion of the camera port through a 15-mm incision on the fifth intercostal space on the midaxillary line. The CO₂ line is connected to the camera port and gas flow is regulated to an intrapleural target pressure of 6 to 10 mmHg; this helps in gaining space early into the procedure, particularly in the left-sided approach, where the camera port is very close to the heart apex. Two additional ports are placed under direct camera vision on the third intercostal space on the midaxillary line, and on the fifth intercostal space on the midclavicular line. Two arms of the da Vinci system are attached to the two access points and another arm is attached to the camera port. The left arm is equipped with an EndoWrist (Intuitive Surgical, Inc.) instrument; the right arm has an Endo-dissector device (Intuitive Surgical, Inc.) with electric cautery function [Figure 1B].

Left-sided approach

The dissection starts inferiorly at the level of the left cardiophrenic angle and continues along the anterior border of the phrenic nerve. All anterior mediastinal tissue, including fat, is isolated from the phrenic nerve. The left inferior horn of the thymus is then located and dissected from the pericardium. Subsequently, the thymic gland is separated from the retrosternal area until the right mediastinal pleura and the right inferior horn are found. At this point, the lower part of the thymus is moved upward, the left innominate vein is identified, and the dissection continues along the border of the innominate vein, up to the point where the thymic veins are identified, clipped, and divided. The dissection continues upward to the neck until the superior horns are identified and divided from the inferior portion of the thyroid gland. The thymus gland, anterior mediastinal, and neck fatty tissues are resected “en bloc”, the medial port incision is slightly enlarged two fingerbreadths, and the specimen is then placed in an Endobag and removed. After hemostasis, a 28F drain is inserted through the medial port, the lung is inflated, and the other wounds are closed. The patient is extubated in the operating room and then sent to the ward.

Table 1. Main published series of robotic thymectomy for myasthenia gravis

Ref.	Year	No.	Approach	Complete remission rate (%)	Morbidity (%)	Mortality (%)
Freeman <i>et al.</i> ^[20]	2011	75	Left	28	6.7	0
Ismail <i>et al.</i> ^[19]	2013	273	Left	57	1.6	0
Marulli <i>et al.</i> ^[21]	2013	100	Left	28.5	6.0	0
Keijzers <i>et al.</i> ^[22]	2015	125	Right	28.2	7.2	0
Kumar <i>et al.</i> ^[23]	2017	71	Left	38	7.0	0

Right-sided approach

The mediastinal pleura is incised just anterior and medial to the right phrenic nerve, starting from the cardiophrenic angle and progressing upwards, and all anterior mediastinal tissue is separated from the nerve and the superior vena cava. The retrosternal parietal pleura is then opened medial and parallel to the right internal mammary vessels, and mediastinal tissue is dissected off the sternum anteriorly and the pericardium posteriorly, until the left brachiocephalic vein is identified. The thymic veins are identified, clipped, and dissected. The superior horns are then identified and divided from the thyroid gland. The left pleura is then opened and after the left phrenic nerve is identified, the dissection of the thymus is completed and the specimen is extracted as described above.

OUTCOMES OF ROBOTIC THYMECTOMY

The safety profile of RATS thymectomy seems excellent, with a morbidity rate ranging between 1.6% to 7.2% and no perioperative mortality in any of the studies [Table 1]. The most commonly reported complications include myasthenic crisis, bleeding and chylothorax^[19-23]. In terms of postoperative results (blood loss, morbidity rate and length of hospital stay), several single-center case series have demonstrated better outcomes with RATS than with open thymectomy^[24-26]. A multicenter study from the French database EPITHOR confirmed that patients undergoing thymectomy with minimally invasive procedures (mostly RATS) had fewer postoperative complications and a shorter hospital stay compared to patients operated on by sternotomy^[27]. However, because of important disparities in baseline patients' characteristics, no firm conclusions about the superiority of one technique over the other could be drawn^[27]. Finally, a recent systematic review compared postoperative outcomes after thymectomy by RATS or VATS, and found no significant difference in terms of morbidity, conversion to open and length of hospital stay^[28].

As far as neurological outcomes are concerned, in general, non-surgical factors that are believed to decrease the effectiveness of thymectomy in palliating symptoms of MG are the presence of thymoma (as compared with thymic hyperplasia), duration of symptoms longer than 1 year, and older age^[29]. The completeness of removal of all thymic foci, on the other hand, is the single most important surgery-dependent variable that influences postoperative neurological outcomes^[10,11]. Unfortunately, because of differences in surgical approaches and operative techniques, it is not always easy to determine the extent of removal of thymic tissue from retrospective studies. In an attempt to overcome this issue, the following definitions have been proposed: basic thymectomy includes the removal of the thymic gland without any surrounding fat; extended thymectomy includes removal of the thymus with surrounding fatty tissue of the neck and the mediastinum^[30]; finally, the maximally extended thymectomy procedure, proposed by Jaretski, consists in removal of the thymus with all mediastinal fat, from the level of the upper poles of the thyroid gland to the diaphragm, with opening of both pleural cavities^[10]. Clearly, the maximally extended procedure is recommended to achieve the highest remission rates. Zielinski and colleagues, in fact, have compared neurological outcomes of patients who underwent thymectomy according to 3 different techniques, demonstrating better complete remission rates in the group of patients treated by the most radical operative technique^[31].

Following robotic thymectomy, all authors report satisfying complete remission rates, with values ranging from 28% to 57%^[19-23]. These results are in line with complete remission rates achieved by transsternal

thymectomy, which range from 15.8% to 60%^[32]. Another neurological outcome measure is the proportion of patients experiencing an improvement of MG symptoms, as defined by the MGFA postintervention status classification, which ranges from 77% to 87.5% in robotic thymectomy series^[20-23]. Again, these figures compare well with those reported after transsternal thymectomy, which leads to palliation rates (defined as symptom-free on medication or minimal symptoms on no medication) varying between 79% and 86%^[29]. Unfortunately, the limited number of patients, the variable inclusion criteria, the different measures used to define the neurological outcomes, as well as differences in operative techniques and surgical approaches, make it impossible to reliably compare neurological outcomes between transsternal and minimally invasive thymectomy, or thymectomy performed by different minimally invasive techniques (e.g., RATS, VATS and subxiphoid). To answer these questions, better designed, multicenter, randomized studies are needed.

CONCLUSION

The benefits of thymectomy for patients affected by nonthymomatous MG have now definitively been proven. RATS is a safe and effective minimally invasive approach to thymectomy, which provides satisfactory neurological outcomes and a reduced surgical morbidity compared to the transsternal approach. The lack of well-designed prospective studies makes it impossible to reliably compare surgical and particularly neurological outcomes between different surgical approaches.

DECLARATIONS

Authors' contributions

Conception and design of the study: Mammana M, Comacchio GM, Dell'Amore A, Rea F

Data analysis and interpretation: Mammana M, Comacchio G, Faccioli E, De Franceschi E, Rossi S

Availability of data and materials

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Technical Note

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Early experience of uniportal video assisted thoracoscopic surgery in a New Thoracic Unit in Hospital Kuala Lumpur, Malaysia

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Abstract

The evolution of video technology and instrumentation have revolutionised the way lung resections are performed without compromising outcomes. In a new thoracic surgery setup, we have adopted the uniportal video assisted thoracoscopic surgery (U-VATS) technique for lung resections in most of our cases. A retrospective review of operative records from July 2017 till June 2019 in Hospital Kuala Lumpur (HKL) for all thoracic surgeries was done. Patients were divided into two groups: those that underwent U-VATS surgery in the first and second year as part of the learning curve. The operative time, blood loss, lymph node yield, duration of drain placement, and length of hospital stay were compared between the groups. The most common indication for U-VATS surgery was malignant lung tumors (21%) followed by ruptured bullae (20%) and empyema thoracis (15%). The average time taken for lobectomies performed for non-small cell lung cancer was 201 min. U-VATS decortication caused the most amount of blood loss with an average of 350 mL, followed by aspergilloma at 315 mL and bronchoplasty at 250 mL. The rest of the procedures had < 150 mL of blood loss. There was no significant difference in the parameters compared between procedures in the two groups. No mortality was seen. The learning curve of U-VATS was used as a guide to gradually increase the complexity of cases performed in a pyramidal manner. U-VATS is an alternative and promising minimal access approach in thoracic surgery that can be safely performed in Malaysia.

Keywords: Uniportal, video assisted thoracoscopic surgery, Hospital Kuala Lumpur, early experience



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INTRODUCTION

Since Giancarlo Roviario performed the first lung resection with video assistance through small incisions without rib spreading in 1992, the evolution of video technology and instrumentation have revolutionised the way lung resections are performed without compromising outcomes^[1]. Diego Gonzales-Rivas popularised the uniportal video assisted thoracoscopic surgery (U-VATS) technique by demonstrating reproducibility of the surgeries and improving patient outcomes. He also performed many complex procedures like segmentectomies and bronchial and arterial sleeves through U-VATS^[2]. In a new thoracic surgery setup, we adopted the U-VATS technique for lung resections in most of our cases. This article will describe our experience through the learning curve of adapting the U-VATS approach in thoracic surgery.

MATERIALS AND METHODS

Operative records of all thoracic surgeries performed from July 2017 till June 2019 in Hospital Kuala Lumpur (HKL) were retrospectively reviewed. All surgeries were performed by a single thoracic surgeon in a newly established thoracic surgery unit. The unit consists of a thoracic surgeon, two thoracic fellows and a surgical house officer. Indications for surgery were mainly infective pleural diseases and tumors (benign and malignant). This and the surgical approach were explained to the patient in detail and consent was taken both for the procedure itself and its recording.

All surgeries were performed under general anaesthesia with single-lung ventilation using a double-lumen endotracheal tube. All patients were positioned in the right or left lateral position, or supine and then cleaned and square draped. The surgeon and assistant would then stand in front of the patient. A 3 to 4 cm incision would be made in the 4th or 5th intercostal space, just medial to the anterior axillary line. No rib spreading manoeuvres were required. A wound protector was applied in all cases. A 10 mm 30° telescope with a high definition video system was used in all patients. VATS instruments were used to assist with the surgeries and up to four instruments could be placed through the uniportal access. Resected tumors were removed with an endobag and a 24 Fr chest drain was then inserted through the same incision for non-infective cases. Two drains, a 24 Fr to the apex and a 28 Fr to the base were inserted for infective cases.

A digitally monitored negative pressure closed drainage system (Topaz Medela) was used for all cases. Drains were removed when the amount of effluent was less than 100 mL. All patients were given patient-controlled anaesthesia with morphine infusion after surgery.

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 21.0 software. The means and standard deviation were calculated for the various parameters. The paired *t*-test was used to compare the means between cases performed in the first and second year after establishment of the unit for the three commonest procedures - bullectomy and pleurodesis, lobectomy and thymectomy.

RESULTS

From July 2017 to June 2019, 320 thoracic surgeries were performed and 169 (53%) were U-VATS surgeries. No biportal or multiportal VATS were performed. The mean age of the patients was 41-years and most (104 of 169, 61%) were males. Amongst the 169 patients, only 57 had no co-morbidities (34%), while the rest had at least one with the commonest being hypertension followed by diabetes mellitus and previous tuberculosis infection.

The most common indication for U-VATS surgery was malignant lung tumors (21%) followed by ruptured bullae (20%) and empyema thoracis (15%). Malignant lung tumors included non-small cell lung cancer (NSCLC) and lung metastasis [Table 1].

Table 1. Patient demographics

Variables	Number (%)
Age (years \pm SD)	41 \pm 21.2
Sex	
Male	104 (61)
Female	65 (39)
Comorbidities	
Diabetes mellitus	27 (16)
Ischemic heart disease	5 (3)
Hypertension	31 (18)
ESRF	5 (3)
COAD	15 (9)
Previous TB	17 (10)
Metastatic disease	12 (7)
No Co-morbidities	57 (34)
Diagnosis	
Empyema thoracis	25 (15)
Ruptured bullae	34 (20)
Haemothorax	11 (7)
Benign lung tumors	15 (9)
Malignant lung tumors	36 (21)
Aspergilloma	9 (5)
Thymic diseases	25 (15)
Ectopic thyroid/parathyroid	6 (3.5)
Diaphragmatic eventration	6 (3.5)
Lung sequestration	2 (1)
Total	169

Categorical variables were reported as frequency counts and percentages. ESRF: End stage renal failure; COAD: chronic obstructive airway disease; TB: tuberculosis.

As shown in Table 2, the commonest U-VATS procedure was bullectomy with pleurodesis. This was followed by lobectomy, thymectomy and decortications. The conversion rate to either a biportal VATS or a mini-thoracotomy was 10%. There was no mortality in U-VATS cases.

Operative time

This varied according to the procedure performed. The average operating time for bullectomy and pleurodesis was 80 min. The longest lobectomy procedure was for aspergilloma, which took 244 min. This is likely because of dense adhesions of the lung to the chest wall and distorted anatomy. Thymectomies were performed via a right U-VATS approach and the average time taken was 147 min.

Comparing the mean operating time between these three procedures in the first and second year, timing is better in the second year but without any significant difference [Table 3].

Blood loss

U-VATS decortication caused the most amount of blood loss at an average of 350 mL, followed by aspergilloma at 315 mL and bronchoplasty at 250 mL. In the first year of performing U-VATS lobectomy for aspergilloma, the mean blood loss was higher than that in the second year although there was no significant difference. The rest of the procedures had < 150 mL of blood loss.

Duration of drain placement and hospital stay

The duration of drain placement for U-VATS procedures ranged between 1 to 7 days. Infective cases such as empyema thoracis and aspergilloma tend to have a longer duration of drain placement compared to non-infective cases such as bullae, NSCLC and thymectomy. Most patients had their drain removed by post-operative day (POD) 3 when the drain amount was less than 100 mL.

Patients undergoing U-VATS for non-infective causes were usually discharged by POD 3 or 4. The longest hospital stay was seen in patients with haemothorax, empyema and aspergilloma undergoing U-VATS procedures, which was around 7 days.

Table 2. U-VATS procedural analysis

Procedures	Number	Operative time (min)	Blood loss (mL)	Lymph nodes	Conversion to open thoracotomy	Drain duration (days)	Hospital stay (days)
Biopsy	11	45	50 ± 10	-	-	1.0 ± 0.8	3 ± 1.0
Hemothorax evacuation + washout	11	85	350 ± 125	-	2 (18%)	3.5 ± 1.7	7 ± 3.2
Bullectomy + pleurodesis	34	80	55 ± 10	-	-	3 ± 1.0	3 ± 1.4
Decortication	25	126	350 ± 110	-	7 (28%)	5 ± 2.5	7 ± 4.2
Wedge resection	6	60	50 ± 11	-	-	1.5 ± 0.9	3 ± 0.8
Segmentectomy	9	170	100 ± 21	4	-	2.4 ± 1	3 ± 1.1
Lobectomy							
Aspergilloma	9	244	315 ± 120	4	1 (11%)	6.8 ± 4	7 ± 3.9
NSCLC	13	201	120 ± 53	20	2 (15%)	3.5 ± 2.2	4 ± 1.5
Lung Sequester	2	180	65	-	-	2.0	3
Metastastectomy	4	120	70 ± 2	-	-	2.1	3 ± 1.1
Bronchoplasty	2	320	250	-	-	4.0	5
Thymectomy	25	147	100 ± 22	3	3 (12%)	2.1 ± 1.1	3 ± 1.8
Diaphragmatic plication	6	130	80 ± 4	-	1 (16%)	2.8 ± 1.9	4 ± 2.1
Ectopic thyroidectomy	3	100	60 ± 12	-	-	2	3 ± 1.4
Ectopic parathyroidectomy	3	120	20 ± 3	-	-	2	3 ± 1.2
Mediastinal mass excision (non-thymus)	5	115	100 ± 18	-	1 (20%)	1.5 ± 0.7	3 ± 2.2
Pericardial window	2	30	10	-	-	3	6
Chest wall resection	1	105	100	-	-	2	3
Total	169				17 (10%)		

Categorical variables were reported as frequency counts and percentages. Continuous variables were reported as means and standard deviation. NSCLC: non-small cell lung cancer; U-VATS: uniportal video assisted thoracoscopic surgery

Table 3. Comparison of U-VATS procedures performed in the 1st and 2nd year

Procedures	Number		Surgery time (min)		Blood loss (mL)		Lymph nodes		Conversion to open thoracotomy		Drain duration (days)		Hospital stay (days)	
Year	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Bullectomy + pleurodesis	18	16	90 ± 22	80 ± 12	52 ± 24	58 ± 20	-	-	-	-	3.0 ± 1.0	3.0 ± 0.9	3 ± 1.0	3.0 ± 0.9
Lobectomy														
Aspergilloma	3	6	260 ± 50	236 ± 35	380 ± 95	283 ± 102	2	2	1	-	7.6 ± 4.0	6.4 ± 4.3	7.6 ± 4.0	6.4 ± 4.3
NSCLC	5	8	219 ± 47	190 ± 25	130 ± 44	114 ± 31	19 ± 3	21 ± 5	2	-	4.4 ± 1.9	3.2 ± 0.4	4.8 ± 1.8	3.5 ± 0.5
Lung sequester	1	1	170	190	60	70	-	-	-	-	2	3	2	3
Thymectomy	11	14	170 ± 33	129 ± 25	110 ± 15	92 ± 22	-	3	3	-	2.5 ± 1.0	1.8 ± 1.0	3.3 ± 2.0	2.8 ± 1.0

Categorical variables were reported as frequency counts and percentages. Continuous variables were reported as mean and standard deviation. There was no significant difference ($P > 0.05$) for the variables between the 1st and 2nd year for all procedures. NSCLC: non-small cell lung cancer; U-VATS: uniportal video assisted thoracoscopic surgery

Only 13 cases of lobectomies for NSCLC were performed by U-VATS in throughout the study duration of two years. The average time taken was 201 min and this includes complete lymphadenectomy of stations 2, 4, 7, 8 and 9 on the right, and 5, 6, 7, 8 and 9 on the left. In the first year of performing U-VATS lobectomies, the mean time taken was 219 min and this reduced to 190 min in the second year with no significant difference between them. The lymph node yield was at the average of 20 lymph nodes with no significant difference between the lobectomies performed in the first and second year [Table 3].

DISCUSSION

Thoracoscopic surgery has been performed via multiple access ports in the thorax since the 1990s. Many publications are available to support the efficacy of this approach^[3-7]. The recently concluded randomised control trial, Video Assisted Thoracoscopic Lobectomy Versus Conventional Open Lobectomy for Lung Cancer (VIOLET) study confirmed that VATS is not inferior to open thoracotomy in the oncological outcomes of NSCLC resection and provides better post-operative pain control. Since 2003, Prof Gaetano

Rocco from Italy has evolved from using three to two and now, a single port for thoracic surgery, performing mediastinal biopsies, wedge resections and bullectomies^[8]. In 2010, Diego Gonzales Rivaz was the first to perform a lobectomy through the uniportal approach and went on to execute complex lung resections over the next few years, including carinal resections^[2]. Perna *et al.*^[9] then performed a randomised trial comparing U-VATS and multiportal VATS procedures in 2016 and found no difference in post-operative pain and analgesia intake, duration of chest drain and length of hospital stay. In the meta analysis by Abouarab *et al.*^[7], it was demonstrated that U-VATS provides superior post-operative outcomes over multiportal VATS.

The advantages of U-VATS are mainly seen in positioning of the videoscope in the utility port to provide an end on view to the surgeon, similar to open surgery. Insertion of instruments parallel to the videoscope also simulates the manner of dissections done in open surgery. Having all instruments inserted via a single incision also reduces post-operative pain by reducing the number of ports and prevents compression of the intercostal nerves by not using thoracoports^[4,10]. Nevertheless, the crowding of instruments inserted through the same port can be an obstacle^[11]. The usage of curved instruments of variable length inserted at different angles can prevent this. Thinner instruments designed specifically for U-VATS allow up to four instruments to be inserted with the videoscope^[1,4] [Figure 1A].

The thoracic unit in HKL was established in July 2017. Thoracic surgeons in Malaysia have vast exposure in laparoscopic surgeries during general surgery training and with this experience, performing VATS becomes easier. In our unit, we perform around six to seven thoracic surgeries a week with almost half performed by U-VATS and the rest were open thoracotomies. No multiportal VATS were performed, hence we are unable to compare with these methods. In our unit, surgeons must be familiar with open thoracotomy first and able to handle emergency situations such as bleeding before performing VATS.

The learning curve of U-VATS could be steeper than multiportal VATS^[11,12]. Attending U-VATS workshops, attachments in high volume centres such as the Shanghai Pulmonary Hospital and watching surgical videos can assist with the improvement of developing U-VATS techniques for beginners and advanced level surgeons^[13,14]. These approaches were adopted by our centre to enhance performance of U-VATS. During the learning process, we developed the U-VATS learning pyramid as a guide for trainees [Figure 2]. The U-VATS learning pyramid gradually increases the complexity of cases from the bottom up. Adapting the U-VATS learning pyramid in a stepwise manner as per the caseload in the centre may allow the learning experience to be smoother and safer for both the patient and the surgeon alike. The initial U-VATS cases that were performed were less complex, such as bullectomy with pleurodesis, traumatic hemothorax evacuation, biopsies and wedge resections. The surgeon should not perform U-VATS lobectomy if he/she has not performed U-VATS wedge resections or bullectomies comfortably before. In the first three months of performing U-VATS, most cases are from the bottom of the pyramid. Attempts to perform U-VATS lobectomy were only made once familiarity with the basic procedures were achieved. This learning pattern is seen in many other centres worldwide in learning uniportal VATS^[3-5].

The effectiveness of the learning pyramid for U-VATS is reflected in our centre having no mortalities in 169 cases performed so far. Although there was no significant difference between cases performed in the first and second year, the duration of surgery appeared to be less for cases in the second year group. This could be due to increased familiarity with handling of instruments and positioning of the camera as more cases are performed. Liu *et al.*^[14] showed that a minimum of 30 cases of U-VATS lobectomy are needed to reach performance plateau.

Our first uniportal lobectomy performed was a left lower lobectomy for lung adenocarcinoma with a nodule measuring 3 cm, however an assistant port was inserted halfway through surgery for retraction

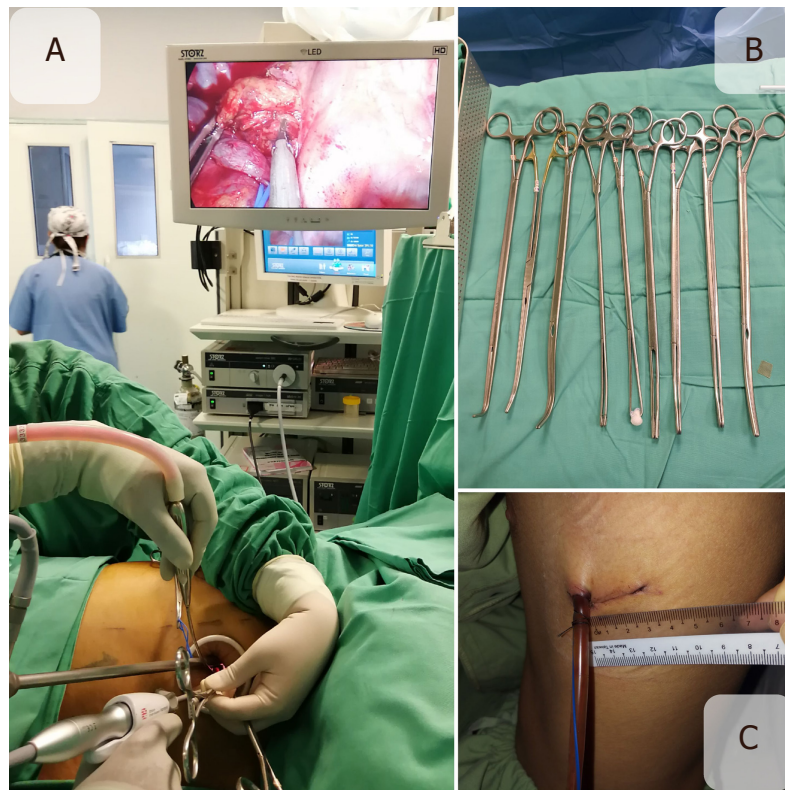


Figure 1. A: the U-VATS method of performing thoracic surgery where multiple VATS instruments are inserted through the same port to complete the resection; B: U-VATS instruments that are long and double hinged; C: the wound size for a U-VATS left upper lobectomy. U-VATS: uniportal video assisted thoracoscopic surgery

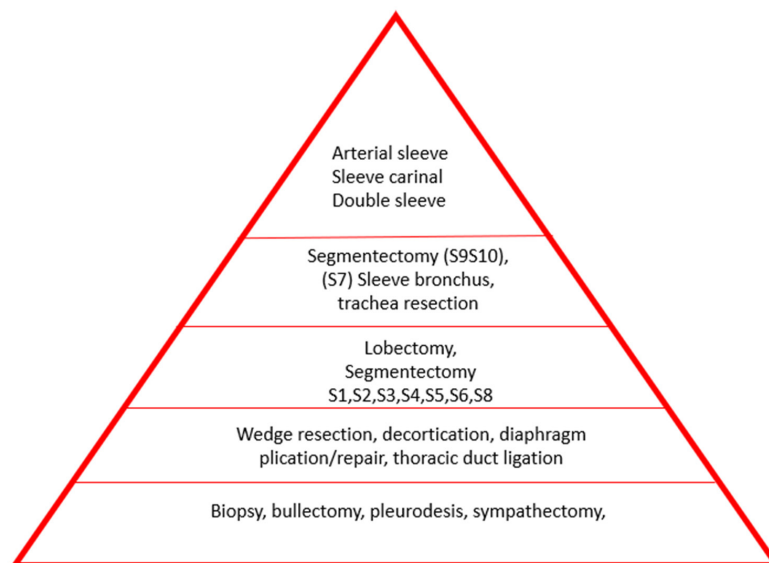


Figure 2. Suggested uniportal video assisted thoracoscopic surgery learning pyramid for adaptation in training

during lymph node dissection. It was a successful surgery that took us 200 min to complete. Subsequent lobectomies were performed without the assistant port. Left lower lobectomy was chosen as our first case to perform because it is easier compared to other lobes^[1]. In 17 cases (10%), we used either an extra port or converted to a mini-thoracotomy due to bleeding, to facilitate retraction or dissection, introduction of

a stapler, completion of lymph node dissection and in some cases, enlargement of the wound to deliver the resected specimen in one piece. Ismail *et al.*^[3] from Germany also reported operating times of around 250 min in their early experience of performing U-VATS for lobectomy.

The average lymph node yield in our U-VATS lobectomy for NSCLC was 20 and this allows adequate staging assessment by the oncologist to decide on adjuvant treatment. This was similarly reported by the Koreans in their midterm outcome of U-VATS for lung cancer^[5]. Crucially, one must not hesitate to introduce a second port during lymph node dissection to achieve adequate yield in the early stages of performing U-VATS lobectomy. Oncological outcomes supersede any chosen approach.

The duration of drain placement usually coincides with the length of hospital stay. Most non-infective cases were discharged by POD 3 or 4 after surgery whereas the infective cases stayed longer. The infective cases also had a higher amount of blood loss compared to lung cancer cases because of the higher degree of adhesion and inflammation and thus, the tendency to bleed more. Compared to open thoracotomy however, the blood loss difference is not significant^[15].

Within two years of performing U-VATS, we have gradually increased the complexities of the surgeries, taking care to minimise morbidities. In the last 6 months, we have performed a left segment 9 and 10 resection for a metastatic lung nodule, and a right upper bronchial sleeve resection for a right main bronchus mucoepidermoid carcinoma successfully. These cases were performed after more than 100 U-VATS cases were logged.

This review was for the first two years since setting up the thoracic surgical services in HKL. We have had a small number of patients involving all procedures, malignant and non-malignant alike. A subsequent review of patients with NSCLC with larger numbers at the 5-year mark will shed clearer light on the advantages of U-VATS in HKL, Malaysia.

CONCLUSION

U-VATS is a promising, alternative approach which is fast gaining popularity amongst thoracic surgeons worldwide. The learning of U-VATS procedures should be in a stepwise manner as suggested in our learning pyramid. Patient safety and oncological principles must always be adhered to in any form of surgery and failing to do so will require an alternative approach. The U-VATS technique may be safely adopted in a new thoracic centre if such a stepwise learning method is enforced.

DECLARATIONS

Authors' contributions

Collected and selected articles: Sathiamurthy N

Participated in manuscript, writing and review: Sathiamurthy N, Diong NC, Dharmaraj B

Participated in reviewing: Sathiamurthy N, Dharmaraj B

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Approval obtained from the Director's office and the hospitals' ethics committee to proceed with this analysis.

Consent for publication

Not applicable.

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Original Article

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Endometrioma surgery and possibilities of early disease control

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Abstract

Aim: The purpose of this study is to investigate the efficacy of surgical management in ovarian endometrioma for early disease control and long-term fertility preservation in adolescents and women of very young age. A history of cyclic pains in adolescents is highly associated with endometriosis. Sonography enables the diagnosis of small endometriomas 1-2 cm in diameter. Although it is obvious that the risk of damage to normal ovarian tissue is diminished when operating and removing a 2 cm endometrioma, it is not approved since there are currently no tools available to identify at-risk patients. Additionally, performing laparoscopic surgery with 5 mm instruments in patients with small endometriomas will likely cause more harm than benefit.

Methods: A literature review was performed using key words for endometrioma surgery, *in vitro* fertilization (IVF), implantation rate, pregnancy rate and adolescents. The pros and cons of surgical removal prior to assisted reproductive therapy (ART), outcomes of endometrioma surgical treatment before IVF, and current recommendations for endometrioma removal were investigated.

Results: The total patient population from articles supporting removal of endometrioma before assisted reproductive therapy and evidence against were 30,741 and 9983 respectively. However, the only study reporting a statistically significant result found an 8.2% implantation rate for the surgical removal group *vs.* 12% in the direct-to-IVF group, and 14.9% pregnancy rate in the surgical removal group *vs.* 24.9% in the direct-to-IVF group. Damage to ovarian reserve and function due to surgery is exacerbated by large cyst size, stripping of the



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pseudocapsule and older age. Larger endometrioma, ablation of the endometrioma base and younger age are associated with higher recurrence rate.

Conclusion: The patient's age, in addition to the size and type of endometrioma, can direct and indicate the timing of surgical management. Bilateral endometriomas and those larger than 7 cm are associated with more damage to ovarian reserve due to disease and surgery, as compared with unilateral lesions and those smaller than 7 cm. High-risk adolescents and very young women seeking fertility treatment can thus benefit from an early diagnosis of endometrioma. Treatment by trans vaginal hydro-laparoscopy of selected cases can probably be suggested for the treatment of small endometriomas, since 5fr instruments are used following microsurgery principles. Therefore, an early diagnosis of endometrioma, especially in young patients, must be encouraged, improved and standardized, through stepwise clinical reasoning and diagnostic testing.

Keywords: Endometriosis, endometrioma, assisted reproductive therapy, *in vitro* fertilization, surgery, adolescents

INTRODUCTION

Endometriomas affect 17%-44% of women with endometriosis^[1]. Approximately 17% of women suffering from infertility are diagnosed with an endometrioma^[2]. The pathogenesis of endometrioma is characterized by sequential and progressive damage of healthy ovarian tissue. During menses, the implantation of regurgitated endometrial cells on the ovarian surface (via tubal lumen) causes a series of biochemical reactions including persistent inflammation, bleeding (at the implantation site) and invagination of the ovarian cortex, adhesions, cystic formations, tissue alterations and deformity^[3]. Invagination of the ovarian cortex secondary to metaplasia of celomic epithelium in the context of cortical inclusion cysts has also been proposed as a possible mechanism of endometrioma formation^[4]. Hence, the endometrioma pseudocapsule itself is ovarian epithelium containing follicular structures and oocytes. Upon opening the endometrioma after irrigation, endoscopic imaging reveals pinkish tissue that is the ovarian epithelium. The ovarian tissue that is identifiable during endoscopic imaging is thus embedded with endometriotic cells that can continue to proliferate and migrate even, if not destroyed^[5].

In addition, ovarian endometriosis, is a marker of more significant pelvic and intestinal endometriotic lesions^[6]. Despite the fact that the diagnosis of an endometrioma can be done by transvaginal ultrasound examination at a very early stage, the identification of patients who will deteriorate through development of larger endometriomas remains a major challenge.

Although cyclic pelvic pain, dyspareunia, bleeding, dysuria and/or infertility are the common presentations, symptoms do not indicate the extent and/or progression of the disease. Endometriosis awareness among general practitioners and the public is still very poor. Misdiagnosis and under-treatment occur not infrequently. As a result, endometriomas are often diagnosed when the cyst is very large, and/or the disease has reached an advanced stage - this is especially the case among adolescent women^[7]. Hence, many infertility patients present with endometrioma and tubal factor problems with an indication for *in vitro* fertilization (IVF) treatment.

A systematic review of the literature was performed to identify the course of action in treating endometriomas prior to IVF. In addition, 9 current guidelines by international gynecological societies were used as a tool to guide identification of the current gaps in research and evidence for clinical practice. Research was also focused on the pros and cons, as well as outcomes of surgical treatment for endometrioma before IVF. Based on the evidence and conclusions of our research, an algorithm for the management options in endometrioma prior to IVF is proposed.

METHODS

Materials

A literature review of internet/online databases and formal papers and presentations was performed. Internet-based resources included the following: (1) search engines: Google and Google Scholar; (2) research databases: PubMed and Ovid Embase; (3) library database: St. George's University of London Hunter Database. Numerous scientific journals both print- and web-based were accessed through these databases. Main titles included: *Fertility & Sterility*, *American Journal of Obstetrics & Gynecology*, *European Journal of Obstetrics & Gynecology & Reproductive Biology*, *Reproductive BioMedicine Online*, *Human Reproduction*, and *PlosOne*.

Methods

Core search terms were: “ovarian endometrioma”, “endometrioma + surgery”, “endometrioma + surgery + IVF”, “endometrioma + Assisted Reproductive Therapy (ART)”. Additional search terms were: “ovarian endometrioma + adolescent”, “ovarian endometrioma + surgery”, “ovarian endometrioma + adolescent + surgery” and “ovarian endometrioma + adolescent + IVF + surgery”. PubMed was used as the primary source of literature due to highest yield of relevant material.

Initial results were further filtered by publication date within 10 years. For the “ovarian endometrioma + adolescent” search, the filter was limited to 5 years as this is a more specific and contemporary research area, with the aim of amassing only the most relevant and current literature. From the final 180 articles, titles and publication dates were used to further distinguish relevant literature and isolate prospective studies. Additional filters were applied to focus on adolescents. [Figure 1](#) outlines the database search process carried out.

A total of 33 articles matching our search criteria were analyzed and categorized into pro/con of endometrioma surgery prior to IVF depending on the evidence presented.

Fourteen articles provided evidence in support of surgical removal of endometriomas prior to ART. There were two retrospective case-control studies, two retrospective cohort studies and one retrospective analysis. Additionally, there was one committee opinion, one scientific impact paper, one pooled analysis, one literature review, one systematic review and two meta-analyses. Notably there were only two prospective studies - a prospective cohort study and a prospective randomized study [\[Table 1\]](#).

Nineteen articles provided evidence against removal. There were seven retrospective studies and six prospective studies. Additionally, there were two meta-analyses, two literature reviews, one systematic review and one scientific impact paper [\[Table 2\]](#).

Five articles provided evidence for both pros and cons of removal of endometrioma prior to IVF, with a combined total patient population of 6088^[8-12]. In seven studies, the research design, number of patients and characteristics, and results extraction were not clear and thus, excluded from our calculations.

For analysis of current evidence on implantation and pregnancy rates between surgical removal of endometrioma and no surgery prior to IVF, only four studies matched the selection criteria. The following exclusion criteria were applied to the search: (1) sample population: women with endometrioma; intervention group: women having surgical treatment prior to IVF; and control group: women with unremoved endometrioma going into IVF; (2) primary outcomes: implantation rate and pregnancy rate; (3) interventional studies (no review papers); and (4) publication date within last 10 years. An exception was made to the fourth criteria in order to include Wong *et al.*^[13] and Garcia-Velasco *et al.*^[14]. The publication date criteria resulted in many relevant studies being excluded. Among the four studies selected, two were retrospective case-control studies^[14,15] and the other two were retrospective cohort studies^[13,16].

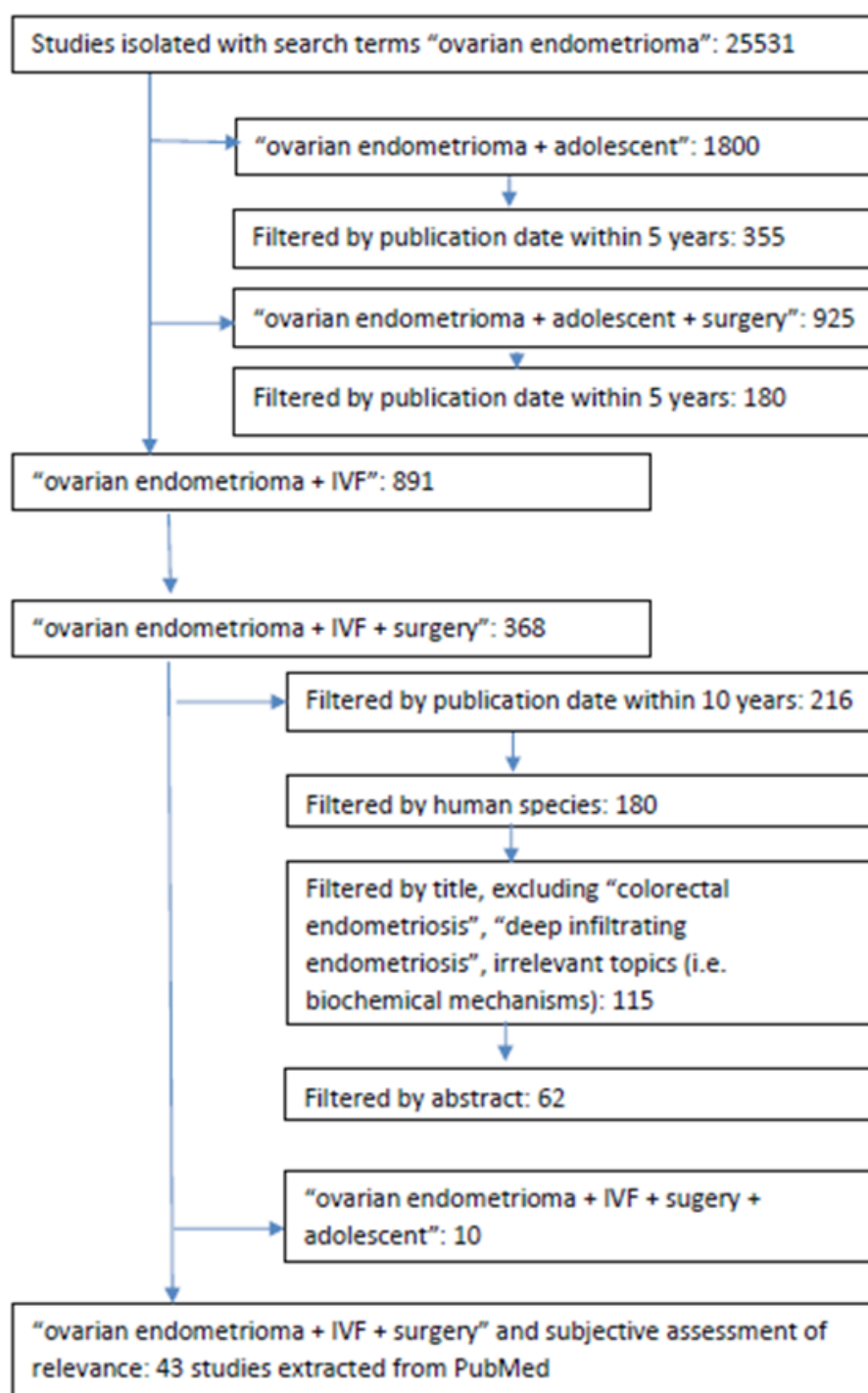


Figure 1. Methodology used to isolate relevant articles on endometrioma surgery prior to IVF and endometrioma surgery in adolescents. IVF: *in vitro* fertilization

Results for the additional investigation into adolescent endometrioma revealed nine relevant articles. Among these articles, three of these were international guidelines, three were review articles, two were retrospective cohort studies, and one was a retrospective case-control study.

Table 1. Pros of surgical removal of endometriomas before ART

Benefits of endometrioma excision prior to IVF	n	Types of Study	Ref.
Risk of ruptured endometrioma, abscess, infection, progression of endometriosis, contamination with endometrioma content	-	Systematic review Committee opinion	Somigliana <i>et al.</i> ^[17] ASRM ^[18]
Contamination of follicular fluid with endometrioma contents can affect IVF outcome	314	Retrospective, case-control study	Benaglia <i>et al.</i> ^[19]
Removal of large (5 cm) endometriomas improves follicular production and number of oocytes retrieved during IVF	26	Retrospective analysis study	Ferrero <i>et al.</i> ^[20]
Removal of large > 4 cm endometriomas can improve fertility outcomes	-	Committee opinion	ASRM ^[18]
Surgical removal of endometriomas > 4 cm increases pregnancy rate and decreases rate of endometrioma recurrence	-	Literature review	Rizk <i>et al.</i> ^[21]
Lower mean oocyte retrieval and higher cycle cancellation rate during IVF/ICSI in women with endometriomas vs. those without	5753 103 64 1039	Meta-analysis Prospective cohort study Retrospective cohort study Meta-analysis	Hamdan <i>et al.</i> ^[10] Ashrafi <i>et al.</i> ^[12] Mao <i>et al.</i> ^[11] Yang <i>et al.</i> ^[22]
No difference in fertilization, implantation and pregnancy rates between pre-ICSI endometrioma surgery and control groups	99	Prospective randomized study	Demiroglu <i>et al.</i> ^[23]
Higher live birth rate post-IVF in patients without endometrioma vs. those with	61	Retrospective cohort study	Benaglia <i>et al.</i> ^[64]
Implantation rate lower in women with endometrioma as small as 0.25 mm vs. women with simple ovarian cyst	168	Retrospective case-control study	Kumbak <i>et al.</i> ^[9]
Surgical removal avoids risk of malignancy associated with endometrioma	- 23,114	Scientific impact paper Pooled analysis of case-control studies	Jayaprakasan <i>et al.</i> ^[8] Pearce <i>et al.</i> ^[24]

ASRM: American Society for Reproductive Medicine; IVF: *in vitro* fertilization; ART: assisted reproductive therapy; ICSI: intracytoplasmic sperm injection

Table 2. Cons of surgical removal of endometriomas before ART

Disadvantages of endometrioma excision prior to IVF	n	Types of Study	Ref.
Surgical removal can result in reduced ovarian reserve	428 - 63 1642 60 291 5753 -	Retrospect case control study Scientific impact paper Prospective case-control study Retrospective analysis Prospective cohort study Meta-analysis Meta-analysis Systematic review	Bongioanni <i>et al.</i> ^[15] Jayaprakasan <i>et al.</i> ^[8] Turkcuoglu and Melekoglu ^[27] Hwu <i>et al.</i> ^[25] Uncu <i>et al.</i> ^[26] Raffi <i>et al.</i> ^[28] Hamdan <i>et al.</i> ^[10] Somigliana <i>et al.</i> ^[29]
Decreased post-surgery pregnancy rates vs. other types of endometriosis	359	Retrospective observational cohort study	Maignien <i>et al.</i> ^[33]
Laparoscopic removal reduces ovarian reserve (low AMH) and increases FSH	193	Prospective study	Alborzi <i>et al.</i> ^[30]
Excision of endometriomas may remove healthy ovarian tissue	326 59	Retrospective cohort study Prospective study	Perlman and Kjer ^[32] Muzii <i>et al.</i> ^[31]
Lower mean number of oocytes retrieved in women with decreased ovarian reserves caused by endometrioma cystectomy vs. idiopathic	167	Retrospective case-control study	Roustan <i>et al.</i> ^[65]
Lower embryo quality and implantation rates associated with endometriotic cyst presence during IVF, potentially caused by disease itself vs. the cystic mass	168	Retrospective case-control comparative study	Kumbak <i>et al.</i> ^[9]
Requirement of higher doses of gonadotrophins for ovarian stimulation post-surgical removal	- 99	Scientific impact paper Randomized control trial	Jayaprakasan <i>et al.</i> ^[8] Demiroglu <i>et al.</i> ^[23]
Ovarian responsiveness and oocyte quality did not significantly differ between endometrioma and non-endometrioma in women undergoing IVF	29	Prospective observational study	Filippi <i>et al.</i> ^[34]
Oocyte quality unimproved after surgery	-	Literature review	Ruiz-Flores and Garcia-Velasco ^[35]
Presence of endometrioma in controlled ovarian hyperstimulation is not associated with reduced absolute quantity of oocytes retrieved from the affected ovary	243	Retrospective case-control study (unilateral endometrioma)	Almog <i>et al.</i> ^[39]
Endometrial receptivity similar in both endometrioma and control groups; no significant impact on implantation, pregnancy rates	103	Prospective cohort study (unilateral/bilateral, < 3 cm)	Ashrafi <i>et al.</i> ^[12]

IVF: *in vitro* fertilization; ART: assisted reproductive technology; AMH: anti-Mullerian hormone; FSH: follicle-stimulating hormone

RESULTS

Pros and cons of surgical removal of endometrioma prior to IVF

The total population across both pro/con, including control and study patients was 40,724.

Pros of surgical removal of endometrioma prior to IVF

The total patient population of articles supporting removal of endometrioma before ART was 30,741. [Table 1](#) summarizes the “pros” of surgical removal of endometrioma prior to IVF according to current evidence.

Three articles provided evidence that removal of endometriomas reduces the risk of abscess and infection. The risk of endometrioma rupture with or without pelvic abscess development is supported by five studies within the systematic review carried out by Somigliana *et al.*^[17]. The American Society of Reproductive Medicine committee opinion^[18] reports that this rupture may result in abscesses, infection and further progression of endometriosis as well as contamination of the ovary or peritoneum with endometrioma content. Contamination of follicular fluid via accidental aspiration of endometrioma contents, which occurred in 19/314 total patients (6.1%), resulted in lower adjusted clinical pregnancy (0.63; 95%CI: 0.49-0.87, $P = 0.005$) and live birth RRs (0.60; 95%CI: 0.51-0.86, $P = 0.003$) amongst the exposed and control groups respectively^[19].

Ten articles, with a combined total patient population of 7313, provided evidence that removal of endometriomas prior to IVF may improve IVF outcomes as measured by the increase in follicular production, oocyte retrieval, fertilization, implantation, and pregnancy rates, and reduced cycle cancellation rates. Three studies found that the removal of large endometriomas improves IVF outcomes^[15,20,21]. One study found that, among patients with unilateral endometriomas measuring > 5 cm, the differences in IVF outcomes between the ovary with endometrioma and the healthy ovary were as follows: (1) less follicles produced in the ovary with endometrioma vs. healthy ovary (total number of follicles: 2.6 +/- 1.3 and 4.8 +/- 2.0, respectively; $P < 0.0001$); (2) less total number of retrieved oocytes (2.0 +/- 1.2 and 4.2 +/- 1.7 respectively; $P \leq 0.01$); and (3) less number of oocytes retrieved which were suitable for fertilization (0.5 +/- 1.1 and 3.3 +/- 1.5 respectively; $P \leq 0.01$)^[20]. Four studies, including a combined total of 6895 patients, demonstrated a lower mean oocyte retrieval during IVF/intracytoplasmic sperm injection (ICSI) in women with endometriomas compared to normal [Standardized Mean Difference = -0.23 (95%CI: -0.37 to -0.10)^[10], (6.6 ± 3.74 vs. 10.4 ± 5.25; $P < 0.001$)^[12], (5.7 ± 3.1 vs. 10.4 ± 4.4; $P < 0.05$)^[11], (Mean Difference = -1.50; 95%CI: -2.84 to -0.15, $P = 0.03$)^[22]]. Among 64 total patients undergoing IVF, comparing 32 cases of endometrioma and 32 tubal-associated cases, there was a higher cycle cancellation rate amongst patients with endometrioma (18.3% and 1.7%, respectively; $P < 0.05$)^[11]. One study compared IVF outcomes in 85 patients with endometriomas measuring 10-50 mm vs. 83 patients with simple ovarian cysts measuring 10-35 mm, found lower implantation rates in women with endometriomas compared to the cyst group (13.9 and 16.4, respectively; $P = 0.03$)^[9]. A randomized control study of 99 patients with endometriomas, randomized to ovarian endometrioma cystectomy pre-ICSI or no surgery, found no statistically significant difference in fertilization (86% and 88%, respectively), implantation (16.5% and 18.5%, respectively) and pregnancy rates (34% and 38%, respectively) between pre-ICSI surgery and control groups^[23].

Two articles, with a combined patient population of 23,114, provided evidence that the removal of endometriomas can also help in the diagnosis of malignancy at an early stage. The lifetime probability of developing ovarian cancer increases from 1% to 2% in the presence of endometriomas^[8]. In their pooled analysis of case-control studies, covering a total patient population of 23,114, Pearce *et al.*^[24] found that endometriosis is associated with increased risk for clear-cell (OR: 3.05; $P < 0.0001$), low-grade serous (OR: 2.11; $P < 0.0001$) and endometrioid invasive (OR: 2.04; $P < 0.0001$) ovarian cancers.

Cons of surgical removal of endometriomas

The total patient population of articles providing evidence against the benefit of endometrioma surgery before ART was 9983. Table 2 summarizes the “cons” of surgical removal of endometriomas prior to IVF according to current evidence.

Evidence that surgical removal of endometriomas damages ovarian reserve and function - reduced ovarian reserve, increased gonadotropin stimulation, lower embryo transfer, implantation and pregnancy rates, increased risk of cycle cancellation - was provided by 16 articles, with a total patient population of 9603. Eight studies provided evidence that surgical removal of endometriomas negatively affects ovarian reserve. These eight studies included a mix of retrospective^[15,25], prospective^[26,27], meta-analysis/systematic review^[10,28,29] and the Royal College of Obstetricians and Gynaecologists scientific impact paper^[8]. Among 1642 women with infertility across three age groups (< 30, 31-35, < 36), there was a lower anti-Müllerian hormone (AMH) in patients with previous endometrioma cystectomy (1.23 +/- 0.15) as compared to patients with endometriomas > 3 cm (2.22 +/- 0.23) and patients with non-endometrioma causes of infertility (3.08 +/- 0.1) ($P < 0.0001$)^[25]. In the retrospective case-control of 428 women undergoing IVF, of which 142 had *in situ* endometrioma at the time of IVF, 112 had laparoscopic endometrioma cystectomy pre-IVF and 174 women had tubal infertility, there were higher cycle cancellation rates in the cystectomy group (7.5% in endometrioma *in situ*, 9.8% in surgery, 2.9% in tubal factor; $P < 0.02$)^[15]. Among 237 patients who were treated for endometriomas via cystectomy, there was a statistically significant decrease in AMH after surgery (mean difference: -1.13 ng/mL; 95%CI: -0.37 to -1.88)^[28]. Another study of 193 patients with endometriomas undergoing laparoscopic cystectomy showed that the surgical removal of endometrioma results in reduced ovarian reserve (pre-operative AMH was 3.86 +/- 3.58; average post-operative AMH by 9 months was 1.83 +/- 2.06; $P < 0.001$)^[30].

Two studies, with a combined total patient population of 385 women with endometriomas showed that excision may remove healthy ovarian tissue. According to a histological analysis of endometrioma tissue from 59 patients, endometriotic tissue can cover up to 98% of the entire cyst wall (median of 60%) and reach up to 2 mm in depth^[31]. Furthermore, proportionally more endometrioma cystectomies disclosed ovarian stroma *vs.* dermoid cystectomies (80.3% and 17.2%, respectively; $P < 0.001$)^[32]. Since their study found higher implantation (28% and 19%, respectively; $P = 0.02$) and embryo transfer rates (79.7% and 70.7%, respectively; $P = 0.03$) in women with simple cysts *vs.* endometrioma, Kumbak *et al.*^[9] proposed that poorer IVF outcomes due to the presence of endometriotic cysts during IVF may be attributable to the disease itself, rather than the cystic mass. Higher doses of gonadotrophin may be required for ovarian stimulation in patients with endometriomas surgically removed pre-IVF *vs.* patients with intact endometriomas^[8]. This is supported by data from the RCT of 99 patients with endometriomas, which found that those who had endometriomas surgically removed pre-IVF required more days of stimulation (14.0 +/- 2.5, $P < 0.001$) as compared with those who went directly to IVF (10.8 +/- 2.6, $P < 0.001$)^[23]. A recent retrospective study investigated ART outcomes in endometriomas *vs.* other types of endometriosis and found that previous endometrioma removal surgery was independently associated with lower pregnancy rates with ART multivariate analysis OR: 0.39 (0.18-0.89; $P = 0.16$)^[33].

Limited benefit of surgery - based on ovarian responsiveness, oocyte quality and endometrial receptivity - was reported by four articles with a combined total patient population of 375. A recent prospective study of women with unilateral endometriomas found no difference in: (1) ovarian responsiveness (3.7 +/- 2.4 and 4.1 +/- 1.7; $P = 0.54$), (2) number of suitable oocytes (3.1 +/- 2.6 and 3.5 +/- 2.3; $P = 0.51$), (3) number of ‘high quality’ embryos (1.8 +/- 2.1 and 1.8 +/- 1.4; $P = 0.00$) and (4) fertilization rate (64% and 64%, $P = 0.96$) between the affected *vs.* intact ovary, respectively^[34]. Additionally, one literature review concluded that despite often lower numbers of oocytes retrieved, oocyte quality remains the same after surgery^[35]. Finally, one prospective cohort study of 103 patients proposed that endometrial receptivity and accessibility

is similar both in the presence of endometriomas and without. When comparing normal and affected ovaries in patients with unilateral endometriomas, there is no statistical significance in the difference in fertilization rates (72.4% and 69.6%, $P = 0.644$)^[12].

Surgical removal of endometriomas to improve fertility in the adolescent population

The few international guidelines which explicitly address treatment of adolescent ovarian endometriomas unanimously present a stepwise treatment plan commencing with medical treatment first, followed by surgical management, and finally combination treatment when necessary. The European Society of Human Reproduction and Embryology 2016 guidelines state that laparoscopy may be indicated in adolescents with chronic pelvic pain who do not respond to medical treatment^[36]. Similarly, in their 2018 statement on adolescent endometrioma, the American College of Obstetricians and Gynecologists recommend conservative surgical treatment, followed by 6 months of GnRH as adjunct treatment if surgical management was inadequate^[37]. In 2019, the Endometriosis Treatment Italian Club also recommended that laparoscopic surgical treatment of endometriomas in adolescents with moderate-severe dysmenorrhea should not be carried out until medical treatment with estrogen-progestins or progestins has been attempted^[38].

Regarding the specific techniques and decision-making for surgical removal of endometriomas in this population, transvaginal hydrolaparoscopy (TVHL) has been recommended in adolescent patients with ovarian endometriomas measuring < 3 cm^[39]. More recently in 2018, Benagiano *et al.*^[40] suggested TVHL for endometriotic cysts measuring < 20 mm and laparoscopic surgical removal of endometriotic cysts measuring > 20 mm in the context of disease that is refractive to medical treatment.

There are very few studies addressing the specific topic of surgical removal of endometriomas for fertility preservation in adolescents. Statistically significant findings from Coccia *et al.*^[16] retrospective cohort study inclusive of women of all reproductive age with endometriomas who underwent IVF/ICSI showed an 8.2% implantation rate for the surgical removal group *vs.* 12% in the direct-to-IVF group, and 14.9% pregnancy rate in the surgical removal group *vs.* 24.9% in the direct-to-IVF group. Additional studies not limited to the adolescent population revealed that older age was found to be associated with lower AMH for both cystectomy and control groups^[25]. Moreover, amongst women who had endometriomas removed surgically pre-IVF, higher pregnancy rates were found among women aged < 35 (34.3%) as compared to women aged > 35 (25.9%)^[41]. One study described an 11-year-old patient with endometrioma who presented initially with amenorrhea and had spontaneous menarche post-surgical removal^[42].

DISCUSSION

Size and type of endometrioma can influence appropriateness of surgical management

Studies have shown that bilateral endometriomas and those larger than 7 cm are associated with more damage to ovarian reserve due to surgery, as compared to those that are unilateral and smaller than 7 cm^[43]. Regarding laparoscopic surgical removal, damage to ovarian tissue may be proportionally related to the size of the endometrioma: excision of cysts measuring > 4 cm results in more significant damage^[44]. Recently, Coccia *et al.*^[16] reported that size is perhaps the most significant factor with regard to ovarian retrieval: for each mm increase in size, there is a decline in predicted number of oocytes retrieved. Bilateral ovarian endometrioma removal presents a worse outcome as compared to unilateral endometriomas: the decline in ovarian reserve, independent of age and destruction of the ovarian parenchyma, still predicts a worse outcome *vs.* unilateral and no surgery^[16]. On the other hand, Ashrafi *et al.*^[12] found in their prospective cohort study that clinical outcomes - such as fertilization, maturation rate and total formed embryos - were no different between unilateral endometriomas and no endometrioma. This is consistent with findings by Yu *et al.*^[45] that there were no significant associations found among laterality of endometrioma, ovarian reserve, and pregnancy outcomes of IVF/ICSI for women with infertility having undergone laparoscopic cystectomy.

Ovarian reserves

Most studies employ the stripping technique to treat endometriomas in order to reduce recurrence, at the expense of significant damage to healthy ovarian tissue. One retrospective cross-sectional study found that AMH was not reduced in patients with endometriomas independently, but that it was reduced in patients with previous endometrioma removal surgery^[46]. However, another study showed that among young women (aged 18-22) there were statistically significant lower median AMH levels even prior to surgery in those with bilateral endometriomas as compared to controls and those with unilateral endometriomas^[47]. In a recent prospective case-control study which compared women without endometriomas, women with endometriomas, and women who had surgical removal of endometriomas, it was found that damage to ovarian reserve increased respectively across all three groups^[27]. This presents the possibility that ovarian reserve damage may be proportional to the extent and frequency of surgery, again, with all employing the stripping technique. In many of these studies, it is suggested therefore to assess ovarian reserve before undertaking surgical removal of endometriomas, and that this factor may be significant enough to recommend against surgical removal. Proper preoperative evaluation, and adequate training and experience of the laparoscopist, are crucial parameters that determine the long-term success of the endoscopic approach^[48,49].

Surgery as a means of preserving ovarian tissue

Surgical removal of endometriomas can enable cryopreservation of ovarian tissue. During surgical removal of endometriomas, healthy fragments of ovarian cortex can be isolated and subsequently cryopreserved, reportedly a highly effective technique for fertility preservation^[50]. Furthermore, Carrillo *et al.*^[50] recommended that ovarian tissue preservation through cryotherapy be individualized based on factors that overlap with those we have identified as priorities for the surgical management of endometrioma: patient's age, ovarian reserve status, presence of bilateral lesions, and repeated surgery. In the adolescent population, ovarian tissue and/or oocyte cryopreservation is especially important to optimize future fertility as suggested by Benagiano *et al.*^[40].

Since endometriomas progressively damage ovarian reserves, it seems logical that the surgical treatment of an endometrioma of a smaller size, preferably lower than 3 cm, would preserve healthy ovarian tissue. The problem is we lack the scientific knowledge to identify those patients that will rapidly deteriorate and develop larger lesions. Gynaecologists who perform TVHL can operate on small endometriomas less than 3 cm with precision and safety using 5Fr instruments^[51].

Adolescent population

Adolescents and very young women with endometriomas present a very high risk of premature ovarian failure and infertility. Endometriomas in adolescents may have a different pathophysiological origin^[40] as well as different manifestation from that of adult endometriosis. The diagnosis of endometriosis in adolescents is often delayed. This delay is attributable to several factors including a puzzling clinical picture such as the presence of both cyclic and acyclic pain^[52], lower proportion of incidental findings (23%) as compared to adults^[53], or lesions which are difficult to identify laparoscopically due to clear color and benign appearances^[37]. Yet, up to 80% of adolescents with chronic pelvic pain refractory to medical treatment end up with a diagnosis of endometriosis^[54]. Currently, the diagnostic pathway involves presence of relevant symptoms (i.e., chronic pelvic pain, dysmenorrhea), response/no response to medical treatment, and finally diagnostic laparoscopy^[37]. Once endometrioma is diagnosed, treatment follows guidelines mentioned previously - surgery is indicated if refractive to medical treatment. There are currently no original studies investigating the early detection and subsequent surgical removal of endometriomas in the adolescent population as it relates to the patients' fertility goals. Much of the existing body of research focuses on older adults because these are the women presenting with concerns for fertility or are actively seeking IVF; however, as endometriosis may often be present but lying dormant and undiagnosed

throughout adolescence, there is a major opportunity for early diagnosis and treatment at the very initial stages when focus of 2-3 mm in diameter of endometriosis appear on the ovarian surface, accompanied by neoangiogenesis and chronic inflammation promoting adhesions, ovarian dysfunction and infertility.

The main concern with regard to endometrioma surgery for adolescents is the high risk of future recurrence. A retrospective cohort study showed that long-term recurrence of endometriosis is higher amongst younger women as compared to older women^[55]. Larger cyst size and younger age were reportedly associated with recurrence in a 2014 retrospective study comparing recurrence rates across subgroups of 550 women with endometriomas^[56]. In their 2017 study of adolescents with endometrioma who had undergone laparoscopic cyst removal via enucleation, Lee *et al.*^[57] found that 16.2% experienced recurrence after first-line surgery, and that recurrence rates increased proportionally to time since surgery. An attempt to strip the pseudocapsule to reduce the risk of recurrence will lead to the destruction of a high volume of healthy ovarian tissue with inadvertent high AMH results and infertility.

Proposal for individualization of management by case identification

Based on the literature, the clinical assessment of endometriomas requires endoscopic establishment of the diagnosis. High-risk adolescents, in addition to older women seeking fertility treatment, can benefit from early diagnosis of endometrioma. It is therefore essential that early identification of eligible patients is improved and standardized, through stepwise clinical reasoning and diagnostic testing as presented in Figure 2.

Modern ultrasound scanning machines enable accurate diagnosis of endometriomas as small as 1.0 cm, depending on the knowledge of the operator and BMI of the patient^[58,59]. In addition to diagnosing endometriomas, the myometrial and the sub-endometrial areas should be meticulously examined, as adenomyosis and adenomyotic cysts may be found; when endometriomas measuring < 3 cm are identified, we should proceed with TVHL. Bigger endometriomas can progress straight to IVF or be treated with laparoscopic surgery. Figure 2 outlines options regarding endometrioma management.

Performing standard laparoscopic surgery using 5 mm bipolar instruments on small endometriomas < 5 cm minimizes the probability of preserving healthy ovarian tissue. Instead, smaller sized endometriomas enable an “easier” operation to be performed that results in less damage to healthy ovarian tissue, such as, surgery with 5F bipolar ball or Argon/Plasma jet laser^[51]. This also reflects the change to transvaginal surgery as a preferable technique over standard laparoscopy in the case of small endometriomas prior to IVF^[51]. Experts in reproductive surgery increasingly support the ablation method using bipolar techniques, avoiding excessive coagulation and carbonization effect^[60]. Carrillo *et al.*^[50] summarized various factors influencing post-surgery ovarian reserve, one of which was the competence of the surgeon as measured by the ability of the surgeon to minimize removal of healthy tissue, identify the extent of endometriotic infiltration and the borders of the lesion, and the ability to minimize coagulation during the procedure. The different treatment options of endometriomas in adolescents and very young women, according to their clinical characteristics are presented in Figure 2.

Recently, Roman *et al.*^[61] proposed using plasma energy ablation as an alternative to cystectomy, finding first in their pilot study of eight women that this technique may spare 90% of healthy ovarian parenchyma that would otherwise be removed during cystectomy. In a subsequent study (30 women with unilateral endometrioma and no previous surgery), they found a statistically significant reduction in ovarian volume and antral follicle count (AFC) ($P < 0.001$) among women who were operated by cystectomy as compared to those operated on by plasma energy ablation. This association was independent of age, previous pregnancy, and endometrioma size^[62].

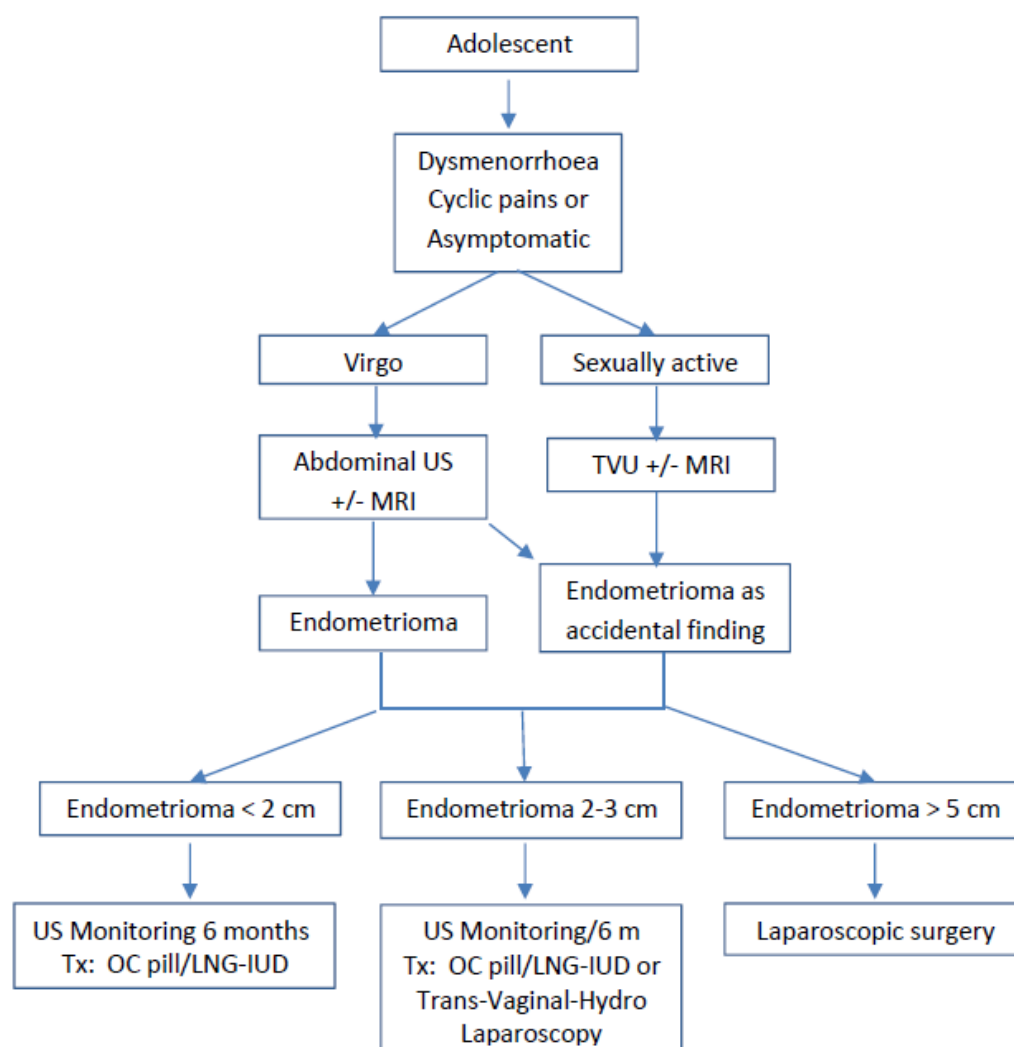


Figure 2. Treatment options for adolescents with endometriomas according to their clinical characteristics. TVU: transvaginal ultrasound; MRI: magnetic resonance imaging; US: ultrasound; OC: oral contraceptive; LNG-IUD: levonorgestrel intrauterine device

Limitations of review

There are important limitations in both the quality and quantity of the available evidence. The lack of randomized control trials (RCTs) investigating surgical management of endometriomas and IVF significantly impacts the quality of evidence. This lack of RCTs results in (1) the inability to have internationally consistent guidelines and (2) a high level of inconsistency and contradiction in the pros and cons analysis of results. Overall, despite endometriosis and endometrioma being two relatively high yield research areas, endometriomas in IVF is a contemporary issue, which is reflected in limited existing data; available data often refer to endometriosis as whole, which resulted in their exclusion from our analysis, and among studies specific to endometriomas there are very limited material evaluating surgical treatment in the context of IVF. This is evidenced by the minimal number of recent studies matching our search criteria on the surgical removal of endometriomas *vs.* non-surgical as pre-IVF treatments (four studies). In addition to these limitations, which affect the yield for adolescent-focused endometrioma research, there is a dearth of studies on the effect on long-term fertility following surgical removal of ovarian endometriomas in adolescents. Despite making exceptions to the exclusion criteria to include more studies, the analysis was extremely limited.

There are specific limitations of the literature to acknowledge. The articles cited in the pros and cons analysis in which there was insufficient information on study size and patient characteristics may have provided biased or skewed data based on unknown factors relating to population characteristics. Regarding the diagnosis of malignancy following surgical removal of endometriomas, for which two articles were cited in [Table 1](#), the majority of available data is limited to theoretical deduction or speculation, rather than statistically significant conclusions due to lack of (prospective studies or RCTs) studies investigating this specific association.

Conclusive remarks

Surgery for endometriosis/endometriomas has a strong potential to increase fertility and optimize ART outcomes under certain circumstances. Surgical outcomes depend significantly on the patient's age, size of endometrioma, interest in fertility preservation, and on the surgeon's skill and experience. Adolescents with endometriomas, considered a high-risk patient population due to delayed diagnosis and vulnerable fertility, stand to benefit from surgical removal not only as it is currently indicated for treatment but also, for long-term fertility preservation. Endometriosis is a very aggressive disease that severely compromises the quality of life and fertility of women, and TVHL can provide an early diagnosis for the treatment of high-risk patients.

Minimal invasive surgery of endometriomas offers safe and effective management. Several reports have demonstrated that recurrent operations of endometriomas, operating on bilateral endometriomas and big endometriomas > 7 cm are associated with diminished pregnancy rates. This evidence must guide the laparoscopic gynaecologist in his/her adjustment and modification of surgical protocols and especially, the timing of operation. Furthermore, endometrioma removal via plasma energy ablation is a relatively new but promising method with regard to both symptom and fertility improvement. A 2019 retrospective study of 21 women showed decrease in post-operative dysmenorrhea, dyspareunia and chronic pelvic pain as compared to preoperative baseline, as well as a 46.2% post-operative pregnancy rate^[63]. While promising, currently there are no clear guidelines regarding ablation as research remains limited due to the lack of robust studies directly comparing ablation to other minimally invasive techniques.

Ultimately, the absence of randomized controlled studies as well as the significant damage to ovarian reserve resulting from the endometriosis disease process itself result in a topic that has garnered significant controversy over the years. An individualized approach to decision making on the surgical removal of endometriomas that is focused on early detection and optimization of ovarian reserve, as well as having a well-trained laparoscopic surgeon, are all essential for guiding management and improving fertility outcomes.

DECLARATIONS

Authors' contributions

Both authors contributed equally to the study.

Made substantial contributions to conception and design of the study and performed data analysis and interpretation, construction of the figures: Tanos V

Performed data acquisition, major writing of the manuscript, as well as provided administrative, technical, and material support: Sowah E

Availability of data and materials

Data supporting the findings can be found in several publications as described in Materials and methods section of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Current state of minimally invasive treatment of locally advanced non-small cell lung cancer

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Abstract

Locally advanced non-small cell lung cancer (NSCLC) has historically been defined as Stage III by the IASCLC staging. While the workup for these patients has been standardized, the treatment algorithms remain unclear. The use of neoadjuvant chemotherapy, radiotherapy, and now immunotherapy still awaits results in terms of optimal regimen. Surgery for local disease control is routinely used and this group of patients have historically been treated with open thoracotomy for resection. Only in the last 10-20 years have minimally invasive surgical methods been applied for treatment. Video-assisted and robotic-assisted thoracoscopic surgery have retrospectively been shown to be safe and effective with equivalent or better perioperative outcomes, long-term overall and disease-free survival, mediastinal lymph node staging to open thoracotomy, and the ability to operate on patients who are too sick for thoracotomy. This review shows that minimally invasive surgery for treatment of locally advanced NSCLC disease should now be routinely offered to patients as the initial surgical method of resection.

Keywords: Locally advanced, minimally invasive surgery, video assisted thoracoscopic surgery, non-small cell lung cancer

INTRODUCTION

Locally advanced non-small cell lung cancer (NSCLC) has been variably defined in the literature from Stage III alone in the 7th edition International Association for the Study of Lung Cancer (IASCLC) staging to the inclusion of the stage groupings of II, IIIA, IIIB, and the newly created IIIC in the 8th edition of the IASCLC Tumor Node Metastasis (TNM) staging^[1,2]. This further breakdown in the 8th edition TNM staging was reflective of the different prognosis for T3 and T4 tumor size associated with N3 nodal disease without metastases. This change means Stage III in the 8th edition of the TNM staging range in size from



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≤ 1 cm to > 7 cm with nodal involvement ranging from none to metastases in the contralateral mediastinal or hilar area, ipsilateral or contralateral scalene area, or supraclavicular lymph nodes^[3]. The new Stage III subgroups were observed to have the following 5-year survival for clinical and pathologic staging, respectively: IIIA 36% and 41%, IIIB 26% and 24%, and IIIC 13% and 12%^[2].

This has led to an update in the clinical practice guidelines available to clinicians. The workup is the same for all Stage III tumors including pulmonary function tests (PFTs), bronchoscopy, evaluation of mediastinal lymph node evaluation, FDG PET/CT, and MRI or CT of the head^[4]. The difference lies in how to proceed afterward. The European Society of Medical Oncology (ESMO) describes a three-pathway approach, whereas the National Comprehensive Cancer Network (NCCN) guidelines describe many more options for management based on the type of Stage III NSCLC cancer^[1,4]. ESMO focuses on nodal status based on preoperative imaging and, while the NCCN guidelines start similarly, the nuance lies with T status, location of primary tumor, presence of multiple tumors, N status, and determination of resectability. Both guidelines are in general agreement that N3 patients and patients deemed unresectable proceed with non-surgical multimodality treatment as their primary management. Incidental or occult N2 disease not previously diagnosed remains a debated topic with NCCN stating that surgery can proceed and then use adjuvant therapy or surgical resection can be halted and neoadjuvant treatment administered before definitive resection^[4]. ESMO suggests proceeding with surgery and then adjuvant treatment^[1]. Both guidelines agree that patients with N0-N1 disease can proceed to surgery first, with caveats in NCCN guidelines regarding location in the thoracic cavity and presence of invasion.

Mediastinal staging is critical as the presence of N2 disease even with tumors of T stage T1a to T1c fall into Stage IIIA^[2]. Staging techniques fall into the three broad categories: imaging, endoscopic, and surgical. De Leyn *et al.*^[5] in their “Revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC” provided an overview of available techniques including Chest CT scan, PET-CT scan, transbronchial needle aspiration, endoscopic ultrasound with aspiration, endobronchial-TBNA, cervical mediastinoscopy, video-assisted thoracoscopic (VATS) biopsy, video-assisted mediastinal lymphadenectomy, or transcervical extended mediastinal lymphadenectomy^[5]. The NCCN recommends any patient suspected of having nodal disease to be biopsied by endoscopic or surgical means^[4].

However, occult N2 disease can still be found even after these techniques. Risk factors that have been identified with occult N2 metastases include larger tumor size and central location as well as high tumor standardized uptake value seen on fluorodeoxyglucose (18F) PET/CT and tumor histology such as adenocarcinoma with micropapillary features^[6-9].

Our review aims to provide a summary of the latest body of knowledge on identification, medical treatment, and surgical approaches to locally advanced NSCLC disease, with a focus on emerging minimally invasive approaches to treatment including video-assisted thoracoscopic surgery and robotic-assisted lung resection.

An extensive literature search was performed by two independent co-authors. PubMed and Cochrane Library were searched from their inception until December 2019. Published manuscripts regarding the management of locally advanced NSCLC were reviewed with regards to the following: tumor characteristics (size, location of tumor, metabolic activity, nodal involvement, clinical and pathologic staging, and final histology), surgical vs. nonsurgical treatment, neoadjuvant or adjuvant therapy around surgery, extent of resection (sublobar, lobectomy, and pneumonectomy), and method of resection (open, VATS, and robotic). We also examined references of articles that we discovered using the previous criteria for additional studies that may not have been found in our initial search. Additionally, articles deemed relevant and not identified in the above-mentioned searches were included after review and consensus by the authors. We excluded all studies that were case-reports, small case-series, or had questionable data analysis.

NEOADJUVANT AND ADJUVANT TREATMENT STRATEGIES

Management of the subset of patients with locally advanced NSCLC remains difficult given their heterogeneous presentations and lack of clear consensus regarding optimal management. Additionally, important distinction should be made between those for whom medical therapy is definitive compared to those considered for surgical resection. Finally, those found to have occult N2 disease following surgery represent a unique treatment dilemma. Current treatment modalities include chemotherapy, radiation, surgery, and immunotherapy with the recent introduction of immune checkpoint inhibitors such as PD-(L)-1 inhibitors. Given the complexity of treatment, a multidisciplinary plan is preferred to optimize care.

Unresectable NSCLC

For unresectable NSCLC as defined by unresectable, node-positive Stage II and Stage III or greater, initial therapy has previously been chemoradiation alone with the American Society of Clinical Oncology endorsing the American Society for Radiation Oncology Evidence-Based Clinical Practice Guidelines which recommend concurrent chemoradiotherapy^[10]. In the past decade, attention has turned to the use of targeted immune therapy as an alternative or in addition to chemotherapy. To date, targeted immunotherapy (excluding check-point inhibitor) has not been shown to improve overall survival in phase III trials for locally advanced NSCLC including most notably the START trial^[11] and INSPIRE trial^[12] for unresectable NSCLC.

Immune checkpoint inhibitors of PD-(L)1 have shown promising results in management of NSCLC. The recent PACIFIC randomized control trial demonstrated that Stage IIIA patients unable to undergo surgery had not only improved progression free survival (23.2 months vs. 14.6 months with placebo; $P < 0.001$), but also overall survival as high as 66% at 24 months with chemoradiation therapy followed by immunotherapy (durvalumab) as compared to chemoradiation alone^[13,14]. Currently, the NCCN recommends this treatment algorithm as standard of care in unresectable disease^[4].

Resectable NSCLC

For potentially resectable NSCLC, the consensus is less clear. All guidelines agree that surgical treatment alone for IIIA NSCLC continues to have a poor 5-year survival and unimodality therapy is not recommended. These findings were demonstrated by two landmark randomized control trials (RCTs), now over two decades old, which demonstrated that the addition of induction chemotherapy to surgery improved overall survival and disease-free survival (median survival 26 months vs. 8 months and median disease-free survival 20 months vs. 5 months for chemotherapy plus surgery compared to surgery alone, which established the standard of care; $P < 0.001$) in Stage III NSCLC patients^[15,16].

Historically, the most debated topic has been the role of surgery in the management of this subset of Stage III lung cancer, IIIA. Initial RCTs such as Intergroup 0139 trial, which enrolled over 400 patients with Stage IIIA NSCLC due to N2 disease to either chemoradiotherapy or surgery, found surgery was not associated with an improvement in overall survival [5-year survival rate, 27% vs. 20%; odds ratio (OR) 0.63; 95%CI: 0.36-1.10]. The intergroup 0139 trial did however find a sevenfold increase in the control of the primary tumors and an improvement in 5-year progression-free survival (PFS, 22% vs. 11%). Of note, in this study, survival was impacted by the high rate of pneumonectomies but there was a clear survival with benefit with surgery for patients requiring lobectomy^[17]. At the same time, the EORTC 08941 study found no difference in overall survival in those who received surgery or radiation following induction chemotherapy^[18]. The latter study was limited as it only enrolled patients with unresectable disease and the rate of incomplete resection was greater than 50%. Most recently, the ESPATUE trial found in IIIA (N2 disease) that 5-year overall survival and progression free survival were equivalent in those who received surgery versus definitive chemoradiotherapy following induction therapy^[19]. In those patients identified as having N2 disease intraoperatively, current NCCN guidelines suggest that those with negative preoperative nodes with

one single positive node found at time of surgery are resectable candidates^[4]. However, the decision to stop and proceed with neoadjuvant therapy upfront continues to be debated amongst clinicians.

The use of targeted immunotherapy as part of multimodality therapy with surgery is less well known. The most recent systematic review of nine eligible trials (eight with surgically resected locally advanced NSCLC) utilizing immunotherapy (excluding immune checkpoint inhibitors) totaling 4940 randomized participants found no statistical survival benefit in overall survival in their pooled meta-analysis (HR = 0.94; 95%CI: 0.83-1.06; $P = 0.35$), and progression free survival (HR = 0.93; 95%CI: 0.81-1.07; $P = 0.19$; high-quality) when compared to conventional therapy except for checkpoint inhibitors such as PD-(L)-1 inhibitors for which results are promising^[20]. Recently, R0 resection has been demonstrated as still being possible in the majority of cases (95%) after immunotherapy, with two recent pilot studies demonstrating no delay in surgery following neoadjuvant nivolumab^[21-23]. Unfortunately, no RCT results are yet available that have examined incorporation of immunotherapy with surgically resectable disease, with four studies (NCT01857271, NCT02201992, NCT02347839, and NCT02595944) created to examine this question with one trial [Erlotinib Hydrochloride Before Surgery In Treating Patients with Stage III Non-Small Cell Lung Cancer (EVENT trial) NCT02347839] closed to poor accrual already (<https://clinicaltrials.gov/ct2/show/NCT02347839>).

In terms of timing of therapy, current guidelines recommend neoadjuvant therapy followed by possible surgery in the appropriate candidate for curative resection if N2 disease is recognized upfront^[4]. Trimodality therapy, consisting of chemotherapy, radiation, and surgery, has been associated with improved median survival and in certain cases has been shown to demonstrate a survival benefit even with Stage IIIB disease ($P < 0.001$) and N3 ($P = 0.010$) in non-randomized trial^[24]. In this regard, one recent meta-analysis by McElroy *et al.*^[25] demonstrated improved survival with neoadjuvant chemoradiation compared to neoadjuvant chemotherapy alone prior to surgery (HR 0.87 vs. HR 1.1, although neither reached statistical significance). However, one phase III trial found no survival benefit with induction chemoradiation compared to induction chemotherapy alone followed by surgery^[26]. To date, there continues to be a lack of consensus regarding utilization of trimodality therapy.

When examining forms of adjuvant therapy, the role of postoperative adjuvant radiation (PORT) is not clear. Initial studies demonstrated a modest benefit in Stage IIIA disease with adjuvant radiation treatment but had limited reduction in local recurrence or survival benefit in early stage disease^[27]. The ANITA III trial is the only RCT to demonstrate increased survival in N2 disease with the addition of adjuvant radiation to chemotherapy (median, 47 months if given radiation vs. 24 months in those without radiation given adjuvant chemotherapy; 23 months vs. 13 months with or without adjuvant radiation in those not given adjuvant chemotherapy)^[28].

For those who may be candidates for adjuvant radiation, survival differences occur based on degree of resection. In a non-clinical trial, PORT was associated with improved survival in R1 resection^[29]. In contrast, a recent meta-analysis found patients treated with PORT have worse survival after R0 resection^[30]. Only one recent study noted a survival benefit in R0 patients if given sequentially following chemoradiation, which has not yet been confirmed by RCT^[31]. The NCCN guidelines currently recommend those found to have occult N2 disease after resection should either receive chemotherapy for R0 resection or combined chemoradiation for R1 or R2 resection^[4].

OPEN THORACOTOMY VS. MINIMALLY INVASIVE SURGERY FOR LOCALLY ADVANCED DISEASE (INCLUDING ROBOTICS)

Thoracotomy has been the standard surgical approach to thoracic surgery, but the past 30 years has seen the development of VATS. While this modality has been further advanced to include robotics, some

contention remains whether VATS is equivalent in terms of safety, lymph node evaluation, and outcomes to open thoracotomy^[32].

Perioperative outcomes

Contemporary studies have demonstrated equivalent or better perioperative outcomes for VATS and RATS^[33-36]. Huang *et al.*^[33] performed one of the earlier studies that called attention to VATS treatment in locally advanced NSCLC. They reviewed 43 patients with Stage IIA-IIIB per UICC 7th edition staging who underwent neoadjuvant therapy from 2006 to 2012 and proceeded on to VATS. Overall, 97.7% of the patients' resections were completed VATS. Blood loss was 253.57 ± 117.08 mL for 28 lobectomies, 5 double lobectomies, 5 wedge resections, 4 pneumonectomies, and 9 sleeve resections. No perioperative deaths were reported. While this study lacked a comparison group, the overall conclusion was that VATS was safe and feasible in this group of patients^[33]. Park *et al.*^[34] soon followed up on this report with a 428-patient study, 397 thoracotomy *vs.* 17 RATS and 14 VATS (referred to as MIS collectively), who had been diagnosed as clinical Stage II and IIIA and underwent surgery after induction therapy. From 2002 to 2013, they noted a conversion rate from MIS of 26% with R0 resection rate of 97% MIS *vs.* 94% open ($P = 0.71$). Complications were similar between groups at 32% and 33% ($P = 0.99$), with more of the open complications related to the cardiovascular system, 11%. Four perioperative deaths were noted in the open group with none in the MIS group. Median length of stay was 4 days in MIS *vs.* 5 days in open ($P < 0.001$). This allowed them to conclude that perioperative outcomes for MIS were equal or better than open surgery^[34]. Veronesi *et al.*^[35] built on this and, similar to Huang *et al.*^[33], focused on RATS for locally advanced NSCLC. In total, 223 patients were retrospectively collected from multiple international sites who were diagnosed as Stage III preoperatively or intraoperatively. They divided the groups into neoadjuvant (15%), adjuvant (63%), and no neoadjuvant/adjuvant treatment (22%). Overall, 10.3% of patients experienced Clavien-Dindo Grade III-IV complications with no difference noted between groups ($P = 0.14$). Overall, 9.9% of cases were converted large tumor size and > 2 positive lymph nodes significantly associated on univariate analysis, which did not carry over to multivariable analysis. Mean hospital length of stay was 5.3 days ($P = 0.641$)^[35]. Lastly, Gonfiotti *et al.*^[36] reported their retrospective review of the Italian VATS Group database, including 3720 early stage patients and 454 locally advanced stage patients who all underwent VATS. They defined locally advanced as cT2b to cT4 in the 7th edition staging and/or received neoadjuvant treatment. They noted a lower estimated blood loss for the advanced stage patients at 169.44 ± 63.69 mL than prior studies but greater than early stage, 186.69 ± 69.65 mL ($P = 0.038$)^[31,34]. Conversions were more common in the advanced stage group (13.0% *vs.* 9.3%, $P = 0.018$); however, bleeding was more commonly the reason for the early stage group, 33.4% (102), while tumor extension was the predominant cause for locally advanced tumors, 25.4% (15). Complication rate was higher in the locally advanced group which was significant, 37.0% *vs.* 30.4% ($P = 0.040$). Thirty-day mortality was not significantly different between locally advanced *vs.* early stage, 1.5% *vs.* 1.6% ($P = 0.880$), nor was length of stay, 7.96 ± 10.10 *vs.* 7.35 ± 29.39 ($P = 0.660$)^[36]. Taken together, these data indicate that perioperatively the outcomes for MIS methods, including for locally advanced NSCLC, is safe with equivalent or better perioperative outcomes.

Lymph node evaluation

Tian *et al.*^[37] focused on lymph node evaluation after neoadjuvant treatment with VATS compared to thoracotomy. For 127 patients, 56 VATS and 71 open from 2000 to 2016, they did propensity matching between the two surgical groups to get 28 pairs to evaluate the sufficiency of mediastinal lymph node dissection between VATS and open. All cases were lobectomies or larger resections. They found no difference in the completeness of resection ($P = 0.611$), but a nonsignificant difference in adequacy of mediastinal lymph node dissection. The guidelines they quoted required evaluation of three hilar and interlobar lymph nodes and three mediastinal lymph nodes from three stations. They noted that 60.7% of the open cases did not meet this guideline while 75.2% of VATS cases did. Most importantly, however, when the lymph node numbers and stations sampled were compared, there was no statistically significant

difference between the two groups. They proceeded to apply multivariable logistic regression and did not find side or surgical technique to be significant predictors for sufficient lymph node dissection; upper or middle lobe location did note a 3.843 hazard ratio for sufficient lymph node dissection ($P = 0.002$)^[37]. Park *et al.*^[34] also demonstrated no difference with their MIS comparison to open, and, although nonsignificant, it trended towards a higher median for lymph node stations sampled in the combined MIS group (RATS and VATS) than the open cohort, 5 (3-7) vs. 4 (1-9) ($P = 0.081$)^[34]. When Gonfiotti *et al.*^[36] compared their locally advanced NSCLC VATS resections to their early stage NSCLC VATS resection, they had more total lymph nodes sampled (15.69 ± 10.47 vs. 13.48 ± 8.18 , $P < 0.001$), more N1 stations sampled (7.55 ± 6.96 vs. 6.38 ± 4.30 , $P < 0.001$), and more N2 stations sampled (8.27 ± 6.62 vs. 7.02 ± 5.58 , $P < 0.001$)^[36]. All this evidence indicates that VATS is at least equivalent to open in terms of lymph node sampling for locally advanced NSCLC.

An additional benefit of VATS as the primary surgical modality is that it can serve as a restaging method before definitive resection. CALGB 39803 was a prospective phase II trial designed to evaluate the possibility of restaging Stage III NSCLC patients, 7th edition TNM staging, after they had undergone neoadjuvant therapy for N2 disease burden. The study was multi-center and ran from 1998 to 2003. The protocol mandated histologically confirmed N2 NSCLC disease and a two-cycle course of platinum-based chemotherapy and/or 40 Gy or more of radiotherapy. Patients then underwent a VATS restaging procedure focusing on signs of pleural carcinomatosis, malignant effusion, or any positive mediastinal node with at least three sampled. Of 68 patients who were evaluated, 20 had no nodal tissue present due to neoadjuvant therapy, 7 had negative nodes, 16 had persistent N2 disease, and 4 had progression to carcinomatosis. This gave a feasibility rate of 69% (95%CI: 57%-80%) for VATS as a restaging modality^[38]. While this study was done, as noted by the authors, before the more regular use of EBUS, this demonstrates that VATS can be used as a restaging modality prior to committing to an open thoracotomy.

Long-term outcomes

Yang *et al.*^[39] published, in 2016, Duke University's retrospective review of 111 cases of Stage IIIA pN2 NSCLC, 7th edition IASCLC staging, who had received induction chemotherapy with or without radiation and then proceeded on to lobectomy. Cases were from 1996 to 2012 with a distinct trend towards increased VATS in later years. They found patients who had undergone VATS had significantly better 5-year overall survival than open surgery, 56.6% vs. 31.4% ($P = 0.007$). No significant difference was noted in recurrence free survival between VATS and open groups, 27.3% vs. 22.3% ($P = 0.17$)^[39]. Yang *et al.*^[40] followed up on this by focusing on VATS vs. thoracotomy after preoperative chemotherapy for any stage NSCLC, including 203 thoracotomy and 69 VATS patients from 1996 to 2012. On univariate analysis, they found significantly better 3-year overall survival for VATS patients vs. open, 61% vs. 43% ($P = 0.010$), but no difference with multivariable analysis despite a trend towards significance, HR 0.56 (0.32-1.01) ($P = 0.053$). Recurrence free survival was no different on univariate or multivariable analysis, 36% vs. 27% ($P = 0.12$) and HR 0.68 (0.42-1.09) ($P = 0.11$). They proceeded with propensity matching on preoperative variables and found no difference on multivariable analysis between VATS and open for overall survival or for recurrence free survival, HR 0.88 (0.39-1.97) ($P = 0.76$) and HR 0.91 (0.46-1.83) ($P = 0.80$)^[40]. Matsuoka *et al.*^[41] from Japan published their institution's experience with 132 patients who had undergone induction therapy before VATS or open and followed them out to 5 years. For the 97 patients they defined as locally advanced Stage II/III, the 5-year overall survival was not statistically different in the VATS vs. open groups, but precise values were not reported ($P = 0.227$)^[41]. Lastly, Park *et al.*^[34] demonstrated similar findings in their RATS and VATS vs. open study with 3-year overall and recurrence free survival being no different, 48.3% vs. 56.6% ($P = 0.84$) and 49.0% vs. 42.1% ($P = 0.19$), respectively^[34]. Taken together, all these studies demonstrate that even in long-term outcomes VATS or RATS is as good as or better than thoracotomy.

Table 1. Actively recruiting clinical trials of neoadjuvant immunotherapy before surgery

National clinical trial number	Country	Patient number	Intervention drug	Study design	Expected completion date
NCT03871153 ^[43]	USA	25	Durvalumab (anti PD-1)	Multi-institutional single arm phase II trial in Stage III (N2) NSCLC to trial concurrent chemoradiation plus Durvalumab induction then surgery then Durvalumab	April 2022
NCT03838159 ^[44]	Spain	90	Nivolumab (anti PD-1)	Randomized, two-arm, Phase II trial in Stage III NSCLC comparing Nivolumab with carboplatin and Paclitaxel then surgery then adjuvant Nivolumab vs. chemotherapy then surgery	September 2027
NCT03197467 ^[45]	Germany	30	Pembrolizumab (anti PD-1)	Single arm, prospective phase II of Stage II/IIIA NSCLC of neoadjuvant pembrolizumab then surgery	2022
NCT03237377 ^[46]	USA	32	Durvalumab (anti PD-1)	Pilot, non-randomized study of Stage IIIA NSCLC of Durvalumab with or without standard thoracic radiation given prior to surgery and followed by adjuvant chemotherapy if deemed appropriate	2021
NCT04025879 ^[47]	113 international locations	452	Nivolumab (anti PD-1)	Phase III, randomized, double-blind trial for resectable Stage II-IIIb NSCLC of neoadjuvant chemotherapy with or without Nivolumab followed by surgery and then adjuvant Nivolumab or placebo	2024
NCT02994576 ^[48]	France	60	Atezolizumab (anti PD-L1)	Single arm, phase II trial of Atezolizumab as induction therapy for Stage IB-IIIa Non-N2 resectable and untreated NSCLC	2022
NCT03732664 ^[49]	China	40	Nivolumab (anti PD-1)	Single arm, feasibility study of neoadjuvant Nivolumab then surgery for Stage IA3 to IIIA NSCLC	2027
NCT02259621 ^[50]	USA	30	Nivolumab (anti PD-1) Ipilimumab (CTLA-4 activation)	Single arm trial of neoadjuvant Nivolumab with or without Ipilimumab for Stage I to IIIA, no N3, NSCLC	2023
NCT03158129 ^[51]	USA	66	Nivolumab (anti PD-1) Ipilimumab (CTLA-4 activation)	Randomized, phase II trial of Nivolumab with or without Ipilimumab then standard induction chemotherapy before surgery for Stage I-IIIa NSCLC	2022

NSCLC: non-small cell lung cancer; PD-(L)1: programmed cell death protein (ligand) 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4

FUTURE DIRECTIONS

Immunotherapy, alone or in combination with traditional chemoradiotherapy, is emerging as one of the next frontiers alongside different methodologies of radiation treatment that could change surgical management of locally advanced NSCLC^[42]. There are currently multiple ongoing trials examining the use of immunotherapy regimens for NSCLC [Table 1]^[43-51]. However, there remains a lack of evidence regarding the safety of pulmonary resection after immunotherapy with only one retrospective study examining surgery after immunotherapy and a Cochrane review on immunotherapy after surgery^[9,18].

CONCLUSION

The treatment of locally advanced NSCLC continues to evolve. Work is ongoing regarding immunotherapy and the best approach: neoadjuvant vs. adjuvant treatment. Additionally, minimally invasive surgical methods continue to evolve and become refined as surgeons increase their experience and technology improves. Although open thoracotomy has previously been the standard for locally advanced NSCLC, VATS is slowly becoming more common as studies show similar long-term outcomes and equivalent or better perioperative outcomes. In our own, unpublished experience, we observed similar rates of complications versus open surgery and shorter length of stay as previously reported but a better rate of proceeding on to adjuvant therapy holding with the concept of faster recovery for less invasive surgery^[52].

This indicates to us that, by performing more cases of locally advanced NSCLC in a minimally invasive manner, we can help patients proceed more quickly to indicated therapy.

While further work is needed to elucidate the appropriate management of locally advanced NSCLC, in terms of neoadjuvant and adjuvant treatment, the minimally invasive surgical approach to this condition has now come into its own. With perioperative, operative, and long-term outcomes now equivalent or better than open thoracotomy, we recommend that experienced surgeons offer minimally invasive VATS approach as the primary surgical method for locally advanced NSCLC.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Dolan DP, Dezube AR, Swanson SJ

Availability of data and materials

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Conflicts of interest

Dr. Swanson is a consultant for Covidien and Ethicon. Remaining authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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Systematic Review

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Robot-assisted minimally invasive esophagectomy: systematic review on surgical and oncological outcomes

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Abstract

Aim: Esophagectomy is associated with several post-operative complications (50%-70%) due to surgical trauma. Minimally invasive techniques have therefore been applied to decrease mortality and morbidity. Robot-assisted minimally-invasive esophagectomy (RAMIE) was developed to overcome the drawbacks of the thoraco-laparoscopic approach. The objective of this systematic review is to report some recent experiences and to compare RAMIE with other approaches to esophagectomy, focusing on technical and oncological aspects.

Methods: Pubmed, Embase and Scopus databases were searched for “robot-assisted esophagectomy”, “minimally invasive esophagectomy” and “robotic esophagectomy” in January 2020. The study was focused on original papers on totally endoscopic RAMIE in the English language. No statistical procedures (meta-analysis) were performed.

Results: Three hundred and twenty studies were identified across the database and after screening and reviewing, 14 were included for final analysis. The overall 90-day post-operative mortality after trans-thoracic esophagectomy ranged from 0% to 9% and did not differ between approaches. Post-operative complications ranged between 24% and 60.9%: respiratory (6.25% to 65%), cardiac (0.8% to 32%), anastomotic leak (3.1% and



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37.5%) and vocal cord palsy (9.1%-35%) were the most frequent. The evidence for long-term outcomes is weak, with no significant differences in overall survival, disease-free survival and recurrence identified in comparison with other approaches. The selected papers showed that RAMIE had comparable outcomes between the open and thoraco-laparoscopic approaches within a multimodal treatment pathway.

Conclusion: RAMIE also seems to be associated with better lymph node dissection, nerve sparing and quality of life, but larger studies are needed to obtain more evidence.

Keywords: Robot-assisted minimally invasive esophagectomy, esophageal cancer, robotic surgery

INTRODUCTION

In the multimodal treatment pathway for esophageal carcinoma (EC), esophagectomy still remains an important component for curative and radical treatment. Current international guidelines^[1-5] recommend combined treatment for patients with localized esophageal or esophagogastric cancer and support the use of minimally invasive surgery such as minimally-invasive thoraco-laparoscopic esophagectomy (MIE) and also RAMIE. Esophagectomy is still associated with several post-operative complications^[5] due to surgical trauma and pre-operative clinical condition of the patient (advanced age, malnutrition, weight loss, chemoradiation). To reduce the consequent mortality and morbidity rates, surgeons have developed minimally invasive techniques also for a complex procedure such as esophagectomy^[6-9].

Furthermore, post-operative and oncological outcomes after esophagectomy are influenced by surgical volume and optimized by referral to specialized centers^[10]. Several concerns have limited acceptance of MIE such as its technical complexity and doubts about its oncological value. The robotic platform (DaVinci system® Intuitive Surgical Inc, Sunnyvale, CA) has several advantages that could overcome the drawbacks typical of MIE such as a magnified and three-dimensional endoscopic view, and articulated instruments with digitally filtered movements^[11]. From the innovative and pioneering experiences of Giulianotti *et al.*^[12] and Kernstine *et al.*^[13], RAMIE has gained popularity amongst surgeons because it seems to ensure adequate oncological outcomes with lower surgical trauma, and fewer post-operative complications in a stable and comfortable environment^[14]. A recent randomized controlled trial (RCT)^[14], a meta-analysis^[15] and some multicenter retrospective studies^[16,17] have demonstrated the safety and oncological adequacy of RAMIE, but other well-designed comparative long-term studies are needed to validate and establish the role of RAMIE.

The objective of this systematic review is to report some recent experiences and to compare RAMIE and other approaches for esophagectomy, with a focus on the technical and oncological aspects.

Technical aspects of RAMIE

Indications

The selection criteria and indications for RAMIE are the same as standard trans-thoracic open or MIE^[8-10] and nowadays, some centers perform it after neo-adjuvant chemotherapy or radiation therapy^[14,15,17]. Relative contraindications to MIE include: poor performance status, impaired lung function to tolerate one-lung ventilation, previous mediastinal surgery or extensive radiation therapy to the mediastinum^[18]. Some types of esophagectomy are available, principally due to localization of the tumor, surgeon preference and the reconstructive options, but the most used are the trans-hiatal and trans-thoracic approaches with reconstruction of the digestive tract in the neck (McKeown esophagogastrostomy) or chest (Ivor Lewis esophagogastrostomy)^[18-22].

Trans-hiatal RAMIE

In this approach, the robotic platform is used only for gastrolisis, abdominal lymph node dissection, esophageal and mediastinal dissection and gastric tube reconstruction^[19]. The anastomosis is performed in the neck^[23,24]. The absence of thoracic incisions seems to be associated with lower post-operative respiratory complications and thus, this procedure could be proposed to patients with comorbidities such as chronic obstructive pulmonary disease and impaired lung function^[19]. The mediastinal lymph node dissection includes only the para-esophageal and subcarinal stations^[19].

Trans-thoracic RAMIE with intrathoracic anastomosis (Ivor-Lewis procedure -ILE-)

With the patient supine, the first abdominal step includes complete mobilization of the stomach, preserving the blood supply from the right gastro-epiploic artery, celiac and splenic lymphadenectomy, hiatal and low mediastinal dissections and finally, gastric tube tailoring. Next, the thoracic phase is frequently performed in a full-lateral left decubitus, semi-prone or prone position with or without single-lung ventilation^[24-27]. The prone position is associated with low pressure capnothorax that could decrease the incidence of post-operative respiratory complications, but some concerns could arise in the event of conversion. Nowadays, the preferred patient position is semi-prone^[14,18,28]. Usually, four or five access ports are used anteriorly to the latissimus dorsi muscle^[14,18,28,29]. The surgical steps are: complete intrathoracic mobilization of the esophagus; para-esophageal, subcarinal and para-tracheal lymph node dissection; and lastly, esophago-gastric anastomosis above or at the level of the azygos vein^[25-29]. Several types of anastomosis can be constructed in the chest and the choice depends on the surgeon's experience, skills and preference. Hand-sewn anastomosis can be performed with the robotic platform, but it did not show clear advantages in terms of reduced incidence of anastomotic leak or stricture, and is associated with longer operative times^[20]. The last Xi DaVinci® platform is armed with robotic staplers and some surgeons have shifted from hand-sewn to mechanical anastomosis^[30].

Trans-thoracic RAMIE with cervical anastomosis (McKeown procedure -MKE-)

Three-field esophagectomy starts with complete mediastinal mobilization, radical thoracic lymphadenectomy and esophageal dissection in the upper region of the chest^[31]. As for the Ivor Lewis procedure, the McKeown's thoracic phase could be performed through the left lateral decubitus or prone position^[21,27,29,30]. After the thoracic phase, gastrolisis, celiac lymph node dissection and gastric conduit construction can be performed in the abdomen^[21,29,30]. The gastric conduit is then pulled-up through the posterior mediastinum and the esophago-gastric anastomosis is performed in the neck^[14,21]. The robotic platform ensures greater exposure for dissection of the upper region of the chest, reducing potential injury to vascular, respiratory (trachea and main bronchi) or nervous structures (vagus and recurrent laryngeal nerves)^[14,32].

Technical aspects of anastomosis

After three-field and trans-hiatal esophagectomy, the preferred techniques of cervical anastomosis are hand-sewn end-to-side and linear-stapled side-to-side anastomosis (modified Collard, Orringer)^[33,34].

According to the literature, esophagogastric anastomosis using the modified Collard method has lower rates of anastomotic leakage (0%-18.4% vs. 0%-27%) and stricture (0%-65.1% vs. 0%-89.9%)^[35].

The minimally-invasive intrathoracic anastomosis is considered a more challenging technique due to the reduced degree of freedom and less space for instrument handling and staplers. However, with the development of new equipment and the evolution of robotic platforms, some intrathoracic anastomosis techniques are now available: hand-sewn^[25,26,36,37], circular-stapled^[28], linear-stapled and trans-oral circular-stapled^[38].

Table 1. Summary of selected papers on robot-assisted minimally-invasive esophagectomy-RAMIE

Author	Year of publication	Type of study	LOE	GOR	Number of patients	Comments
Boone <i>et al.</i> ^[18]	2009	Retrospective study	3b	C	47	One of the largest series of RAMIE for EC published before 2010 with some technical pitfalls and details
Puntambekar <i>et al.</i> ^[27]	2011	Retrospective study	4	D	32	Retrospective study of RAMIE in prone position
Dunn <i>et al.</i> ^[19]	2012	Retrospective study	3b	D	40	The largest series of RAMIE with the trans-hiatal approach, focusing on post-operative and mid-term oncological outcomes
Sarkaria <i>et al.</i> ^[21]	2012	Retrospective study	4	D	21	Retrospective study of patients enrolled over one year in a tertiary center
Suda <i>et al.</i> ^[32]	2012	Retrospective study	3b	C	36	Technical report on RAMIE for SCC focusing on lymph node dissection
de la Fuente <i>et al.</i> ^[36]	2013	Retrospective study	3b	C	50	Retrospective study on Ivor-Lewis RAMIE in a referral center
Yerokun <i>et al.</i> ^[39]	2016	Retrospective propensity matched study on NCDB	3b	C	231	Population-based analysis of RAMIE using a national database; comparison between OE and MIE with regard to post-operative outcomes and 3-year survival
Weksler <i>et al.</i> ^[17]	2017	Retrospective propensity matched study on NCDB	3b	C	581	Population-based analysis of RAMIE using a national database; comparison between OE, MIE and RAMIE on survival
van der Sluis <i>et al.</i> ^[14]	2018	Randomized controlled trial	1b	A	112	The only RCT published which compared OE and RAMIE on post-operative and oncological long term outcomes
Harbison <i>et al.</i> ^[16]	2019	Retrospective study on ACS-NSQIP database	3b	C	725	Retrospective analysis of a national database comparing RAMIE with MIE on morbidity and mortality
Yang <i>et al.</i> ^[22]	2019	Retrospective propensity matched study	3b	C	652	Large retrospective study which compared MIE and MKE-RAMIE on post-operative results and mid-term oncological outcomes
Tagkalos <i>et al.</i> ^[28]	2019	Retrospective study propensity matched study	3b	C	100	Comparison between ILE-RAMIE and ILE-MIE on post-operative outcomes
Sarkaria <i>et al.</i> ^[31]	2019	Prospective, non-randomized trial	2b	B	106	Prospective trial which compared OE and RAMIE focusing in particular on post-operative outcomes, functional assessment and quality of life
Yun <i>et al.</i> ^[29]	2019	Retrospective study propensity matched study	3b	C	371	Large retrospective analysis of the comparison between RAMIE and OE for SCC on post-operative outcomes and mid-term survival

RAMIE: robot-assisted minimally-invasive esophagectomy; LOE: level of evidence; GOR: grade of recommendation; EC: esophageal cancer; SCC: squamous cell carcinoma; NCDB: National Cancer Data Base; ACS-NSQIP: American College of Surgeons-National Surgical Quality Improvement Program; OE: open esophagectomy; MIE: minimally-invasive esophagectomy; RCT: randomized controlled trial; MKE: McKeown esophagectomy; ILE: Ivor-Lewis esophagectomy

Large studies are needed to determine which technique is associated with less anastomotic complications, even if a group reported the shift from hand-sewn end-to-side intrathoracic anastomosis to linear-stapled, reducing the post-operative leak rates^[30].

METHODS

Literature search

Pubmed, Embase and Scopus databases were searched for “robot-assisted esophagectomy”, “minimally invasive esophagectomy” and “robotic esophagectomy” in January 2020. This search was focused on original papers on totally endoscopic RAMIE (systematic reviews and papers about hybrid procedures were excluded) in the English language. Articles were screened for the type and year of publication, first author, number of patients, pre- and post-operative characteristics, post-operative complications and oncological outcomes by the authors Bongiolatti S and Farronato A. Baseline characteristics for all included studies

Table 2. Study type, year of publication and main characteristics of the included studies

Author	Type of esophagectomy	Conversions	EBL (mL)	Type of anastomosis
Boone <i>et al.</i> ^[18]	TT MKE	7 (15%)	625	Cervical handsewn end-to-side
Puntambekar <i>et al.</i> ^[27]	TT MKE	0	80	NA
Dunn <i>et al.</i> ^[19]	TH	5 (12.5%)	97.2	Cervical mechanical end-to-end
Sarkaria <i>et al.</i> ^[21]	TT ILE+MKE	10 (48%)	307 cm ³	Mechanical circular endo-to-end (ILE) Cervical handsewn end-to-side (MKE)
Suda <i>et al.</i> ^[32]	TT MKE	NA	144	Cervical handsewn end-to-side or cervical handsewn end-to-end
de la Fuente <i>et al.</i> ^[36]	TT ILE	NA	146	NA
Yerokun <i>et al.</i> ^[39]	NA	28 (12.1%)	NA	NA
Weksler <i>et al.</i> ^[17]	NA	6.7%	NA	NA
van der Sluis <i>et al.</i> ^[14]	TT MKE	3 (5%)	120	Cervical handsewn end to side
Harbison <i>et al.</i> ^[16]	TT	11 (11%)	NA	NA
Yang <i>et al.</i> ^[22]	TT MKE	2 (0.7%)	211	Cervical mechanical end-to-end
Tagkalos <i>et al.</i> ^[28]	TT ILE	NA	NA	Cervical mechanical end to side
Sarkaria <i>et al.</i> ^[31]	TT ILE+MKE	NA	250	NA
Yun <i>et al.</i> ^[29]	TT MKE+ILE	3 (2.3%)	110	Mechanical circular

EBL: estimated blood loss; TT: trans-thoracic; MKE: McKeown esophagectomy; ILE: Ivor-Lewis esophagectomy; NA: not available; TH: trans-hiatal

are summarized in Table 1. No formal statistical procedure (meta-analysis) was performed. One study was a RCT^[14], and the other 13 were observational studies including one prospective^[31] and 12 retrospective studies published from 2009 to 2019. In addition, four papers had propensity-matched analysis^[22,28,29,39] and three were multi-center studies^[16,17,39].

RESULTS

Three-hundred and twenty studies were initially identified from the electronic databases and after screening and reviewing, 14 were included for final analysis. Table 2 shows the main characteristics of the included studies.

Intra and post-operative outcomes

Conversion rates were reported in ten papers and were much different from the early experience to the latest study [Table 2]. The largest multi-center studies, published in 2016 and 2017, showed a conversion rate ranging from 6.7% to 12.1%; in the RCT, the rate is lower (5%), probably due to the large experience gained by the Dutch group^[14]. Operative time is significantly longer for RAMIE in comparison with open esophagectomy (OE)^[14,29,31] and MIE^[16,22,29].

Dunn *et al.*^[19] in 2012 demonstrated the feasibility of the trans-hiatal approach in a cohort of 40 patients with 2.5% mortality at 30 days, but there was quite a high incidence of overall post-operative complications: anastomotic leaks without the need for re-operation ($n = 10$, 25%); recurrent laryngeal nerve injuries ($n = 14$, 35%) and pneumonia ($n = 8$, 20%) [Table 3]. The use of this approach has gradually decreased in favor of trans-thoracic esophagectomy because the lymph node dissection is more extensive with trans-thoracic esophagectomy and more accurate surgical and pathological staging could be obtained. Trans-hiatal MIE or RAMIE could be useful approaches in patients with severe lung function impairment or other relevant co-morbid conditions because one-lung ventilation and thoracic incisions are not required^[9].

The overall 90-day post-operative mortality rate after trans-thoracic esophagectomy was reported in ten papers and ranged between 0% to 9% without any difference between two or three field esophagectomy^[14,16-19,22,28,29,31]. The RCT published by van der Sluis *et al.*^[14] reported comparable in-hospital mortality rates between patients who underwent RAMIE (2%) and OE (4%) ($P = 0.62$). The 90-day mortality rate was not significantly higher for RAMIE patients (2% vs. 9%; $P = 0.11$). Multicenter analysis by Harbison *et al.*^[16]

Table 3. Post-operative outcomes of RAMIE

Author	Post-operative mortality 90day	Complications				
		Overall	Respiratory	Anastomotic	Cardiac	VCP
Boone <i>et al.</i> ^[18]	3 (4.05%)	NA	21 (44.7%)	10 (21.3%)	6 (12.7%)	9 (19.1%)
Puntambekar <i>et al.</i> ^[27]	NA	NA	2 (6.25%)	3 (9%)	NA	NA
Dunn <i>et al.</i> ^[19]	1 (2.5%)	NA	26 (65%)	10 (25%)	NA	14 (35%)
Sarkaria <i>et al.</i> ^[21]	1 (5%)	5 (24%)	NA	3 (14%)	NA	3 (14%)
Suda <i>et al.</i> ^[32]	0	8 (50%)	1 (6.25%)	6 (37.5%)	1 (6.25%)	6 (37.5%)
de la Fuente <i>et al.</i> ^[36]	NA	14 (28%)	5 (10%)	2 (4%)	5 (10%)	NA
Yerokun <i>et al.</i> ^[39]	NA	NA	NA	NA	NA	NA
Weksler <i>et al.</i> ^[17]	7.8%	NA	NA	NA	NA	NA
van der Sluis <i>et al.</i> ^[14]	5 (9%)	32 (59%)	17 (32%)	13 (24%)	17 (32%)	5 (9.1%)
Harbison <i>et al.</i> ^[16]	3 (3%)	31 (31%)	11 (11%)	14 (14%)	NA	NA
Yang <i>et al.</i> ^[22]	0	122 (45%)	71 (25.3%)	32 (11.8%)	9 (3.3%)	79 (29%)
Tagkalos <i>et al.</i> ^[28]	(5%)	NA	(12%)	(12%)	NA	NA
Sarkaria <i>et al.</i> ^[31]	1 (1.56%)	39 (60.9%)	NA	2 (3.1%)	5 (7.8%)	2 (3.1%)
Yun <i>et al.</i> ^[29]	0	49 (37.7%)	NA	4 (3.1%)	1 (0.8%)	33 (25.4%)

VCP: vocal cord palsy; NA: not available

showed similar mortality between RAMIE and MIE (3% vs. 2.24%); other large retrospective studies have demonstrated that RAMIE had similar mortality rates when compared with MIE and OE^[22].

Post-operative complications were reported in eight studies and ranged between 24% and 60.9%^[14,16,21,22,29,31,32]. Although it can now be performed through a minimally invasive approach, esophagectomy is still associated with a high incidence of overall complications. In the RCT, the overall complication rate was assessed at 59%^[14]; Harbison *et al.*^[16] reported an overall morbidity rate of 31%, while other large single-institution studies reported variable rates from 45%^[22] to 37.7%^[29].

The absence of thoracotomy did not avoid respiratory complications, which were reported in 6.25% to 65% of cases^[14,16,18,22,27,39]. Some possible mechanisms could be involved: prolonged one-lung ventilation, reduced cough reflex due to vagus nerve injury, alteration of swallowing and consequent aspiration, and the presence of comorbidities such as advanced age and chronic obstructive pulmonary disease^[14,16,18,22,27,39]. Cardiac arrhythmias were frequent and reported in 0.8% to 32% of cases^[18,22,29].

Anastomotic complications are still the Achilles' heel of MIE and RAMIE. No subtype (mechanical vs. hand-sewn, end-to-end vs. end-to-side) nor location (cervical or intrathoracic) of esophagogastric anastomosis have shown to be more reliable and safer than others and even after RAMIE, the anastomotic complication rate is still significant and ranges between 3.1% and 37.5%. Although data about anastomotic leak rates are available in most studies, anastomotic stricture is less frequently reported even if it has a negative impact on the quality of life. The RCT^[14] described the need of anastomotic dilatation in 52% of patients who underwent RAMIE, while other single institutional reports showed lower rates of stricture or anastomotic dilatation (4.7%) and the majority of these patients underwent intrathoracic anastomosis^[21].

Although the robot-assisted platform has a magnified three-dimensional view, recurrent laryngeal nerve palsy was described in eight papers and it was frequently reported after cervical anastomosis (9.1%-35%), probably due to extensive lymph node dissection. Chylothorax is another frequent complication and assessed from 0% to 17%^[14,21,22,29]; in the RCT, 4% of patients needed re-intervention for chylothorax^[14]. Some centers perform a prophylactic thoracic duct ligation just above the diaphragm between the descending aorta and esophagus^[14,27].

Only two studies have focused their attention on quality of life after RAMIE, reporting controversial results: Sarkaria *et al.*^[31] evaluated the quality of life using the Functional Assessment of Cancer Therapy-

Table 4. Post-operative and long-term oncological outcomes.

Author	Induction therapy	Tumor type	Mean n dissected lymph nodes	Radicality	3yOS	5yOS	DFS
Boone <i>et al.</i> ^[18]	3 (4%)	ADC 29 (61.7%) SCC 18 (38.3%)	29	36 (76.6%)	NA	NA	NA
Puntambekar <i>et al.</i> ^[27]	NA	NA	NA		NA	NA	NA
Dunn <i>et al.</i> ^[19]	17 (42,5%)	ADC 36 (90%) SCC 2 (5%)	20	94.7%	NA	NA	NA
Sarkaria <i>et al.</i> ^[21]	16 (76%)	ADC 18 (85%) SCC 3 (14%)	20	17 (85%)	NA	NA	NA
Suda <i>et al.</i> ^[32]	NA	SCC 100%	37.5	14 (87.5%)	NA	NA	NA
de la Fuente <i>et al.</i> ^[36]	35(70%)	ADC 46 (92%) SCC 3 (6%)	20	100%	NA	NA	NA
Yerokun <i>et al.</i> ^[39]	120 (70.6%)	ADC 186 (80.5%) SCC 45 (19.5%)	16	NA	NA	NA	NA
Weksler <i>et al.</i> ^[17]	412 (70,9%)	ADC (78.3%) SCC (21.7%)	16	553 (95.2%)	48 months	48 months	NA
van der Sluis <i>et al.</i> ^[14]	49 (94%)	ADC 41 (76%) SCC 13 (24%)	27	50 (93%)	50%	50%	26m
Harbison <i>et al.</i> ^[16]		ADC 68 (68%) SCC 8 (8%)	NA	NA	NA	NA	NA
Yang <i>et al.</i> ^[22]	30 (10.7%)	NA	19.3	263 (93.9%)	NA	NA	NA
Tagkalos <i>et al.</i> ^[28]	NA	NA	27	NA	NA	NA	NA
Sarkaria <i>et al.</i> ^[31]	48 (75%)	ADC 59 (93.7%) SCC 4 (6.3%)	25	62 (96.9%)	81.7%	NA	NA
Yun <i>et al.</i> ^[29]	21 (16.2%)	SCC 130 (100%)	39	127 (97.7%)	81.7%	NA	49.2%

3yOS: three years overall survival; 5yOS: five years overall survival; DFS: disease-free survival; ADC: adenocarcinoma; SCC: squamous cell carcinoma; NA: not available

Esophageal (FACT-E) and Functional Assessment of Cancer Therapy-General (FACT-G) scores, demonstrating a return to pre-operative values only after four months, without difference between OE or RAMIE. van der Sluis *et al.*^[14] administered some validated questionnaires (Short Form-36, EORTC-European Organisation for Research and Treatment of Cancer-Quality-of-life Questionnaire Core 30, EORTC QLQ-OES18-Quality of Life Questionnaire Oesophageal Cancer Module-and EQ-5D-EuroQoL-5-Dimension) at discharge and six weeks after esophagectomy, demonstrating that functional recovery after RAMIE was better and faster than after OE.

Oncological outcomes

Long-term outcomes after RAMIE are still scarce, but data from a large multi-center study^[17] and from the only RCT^[14] showed encouraging results [Table 4]. Trans-thoracic esophagectomy seems to ensure more extensive lymph node dissection than the trans-hiatal approach and in particular, the mean number of retrieved lymph nodes was reported between 5 and 39. Furthermore, trans-thoracic esophagectomy was associated with a complete resection rate between 76.6% and 100%. On the other hand, few papers have reported long-term oncological results: the only RCT^[12] showed that there were no statistically significant differences between OE and RAMIE in overall survival (OS) (log rank $P = 0.427$) at 40 months of follow-up. Moreover, the authors demonstrated no statistical differences regarding disease-free survival (DFS) (26 for RAMIE vs. 28 months for OE) and recurrence pattern.

In their analysis of the National Cancer Data Base (NCDB), Weksler *et al.*^[17] showed 48 months of overall survival after RAMIE, this outcome was not different in comparison with the oncological results obtained by OE and MIE also after the propensity-matched analysis ($P = 0.121$ and $P = 0.53$). With the magnified view and extreme precision of the articulated instruments, RAMIE is increasingly being used after induction treatments: in the RCT, 79% of patients were previously treated with chemo-radiation and in other studies, a large portion of patients were treated before surgery with chemotherapy alone (70.9%-75%)^[16,17] or combined treatments (68%-75%)^[17,21,39].

Dunn *et al.*^[19] in 2012 achieved 94.7% of radical resection with a median of 20 lymph nodes retrieved and a median overall survival of 20 months after trans-hiatal RAMIE. Another paper regarding laparoscopic trans-hiatal esophagectomy showed a median overall survival of 28 months with 3.7% of local recurrence, 22% regional and 37% distant recurrence^[23].

DISCUSSION

RAMIE has gained popularity in the past decade due to increased experience in Western countries and the availability of the robotic platform through Eastern countries, where the incidence of esophageal carcinoma is higher. Large multi-center studies and RCTs have demonstrated that minimally-invasive esophagectomy is safe and oncologically adequate, but it is a technically demanding procedure due to drawbacks from thoracoscopy and laparoscopy^[1,5-9].

The robot-assisted approach has some advantages over the thoraco-laparoscopic one: first, the magnified and three-dimensional intra-corporeal view; secondly, better dexterity due to the articulated instruments with tremor filtering, which allows fine dissection of mediastinal and abdominal structures; and finally, longer instruments with the fulcrum inside the body instead of the abdominal or chest wall, which could decrease post-operative pain. On the other hand, the lack of tactile feedback, longer operative time and costs are the main reported disadvantages of RAMIE. The latest version of the available robotic platform (DaVinci Xi), has four arms that work in a more parallel way than the previous version and with longer instruments, that facilitates meticulous dissection in narrow fields such as the esophageal hiatus and the upper region of the thorax^[10,14,40]. The visceral and lymph node dissections in the cervico-mediastinal outlet could be more accurate and ergonomic with the RAMIE approach, avoiding injuries to other nervous, vascular or respiratory structures. Furthermore, these characteristics have a significant impact on lymph node dissection such that it can be performed in a safe manner due to the magnified view of the operating field and the small instrument tips. Some studies have demonstrated that lymph node dissection in the celiac area, subcarinal and paratracheal is safe and oncologically adequate with reduced nerve injury with RAMIE^[32].

Moreover, for tumors of the esophagogastric junction or lower thoracic esophagus, the robotic platform permits easy handling of instruments to perform hand-sewn or mechanical intrathoracic anastomosis^[20,21,25,26,36]. Anastomotic leak is still the Achilles' heel of esophagectomy and no anastomotic subtype was superior in terms of leakage or stricture. Some factors are associated with anastomotic leaks and a poorly perfused conduit is a well-known risk factor for anastomotic dehiscence. This issue could be reduced with the use of NRF (Near InfraRed Fluorescence) associated with the intravenous administration of indocyanine green. With NRF, the surgeon could obtain a real-time gastric conduit perfusion, identifying inadequately perfused or ischemic areas and then the surgeon could construct the esophagogastric anastomosis on a well-perfused conduit^[30,41]. Moreover, the latest robotic platform is armed with robotic staplers and the surgeon can create a mechanical end-to-side esophagogastric anastomosis with easier handling.

Although evidence about RAMIE are still weak, data from large institutional studies and from the only published RCT supported the application of RAMIE in the treatment of EC in a multimodal treatment pathway^[3,4,10,42]. Some recent papers reported a variable, but high use of induction chemotherapy and chemoradiation therapy with potentially improved long-term results. Long-term OS and DFS were evaluated in few papers, but RAMIE was demonstrated not to be inferior to MIE or OE^[14,17,22,31].

The main issue of robot-assisted surgery remains the high costs to buy the platform and instruments, to start a program and for periodical technical assistance. The actual monopoly of Intuitive Surgical is

undesirable, but competitors are now present on the market and could improve developments, diffusion of ideas and decreasing the costs of robot-assisted surgery.

In conclusion, although possible with a minimally-invasive approach, trans-thoracic esophagectomy is still associated with significant post-operative complications. It has demonstrated acceptable oncological outcomes in terms of radicality, lymph node dissection, overall and disease-free survival. The robotic platform has shown some advantages in lymph node dissection, nerve sparing, improved intra-thoracic anastomosis and faster recovery after surgery, but large studies are necessary to understand the actual role of RAMIE in the multimodal treatment of EC.

DECLARATIONS

Authors' contributions

Conceptualization: Bongiolatti S

Data collection: Bongiolatti S, Farronato A

Formal Analysis, investigation, methodology, project administration, resources and software: Bongiolatti S

Supervision: Bongiolatti S, Voltolini L

Validation and visualization: all authors

Writing-original draft and writing-review and editing: Bongiolatti S

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Early lessons on assembling a center for bariatric endoscopy

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Abstract

As the obesity epidemic continues to grow, the need for effective management strategies is more important than ever. There are several medical, endoscopic, and surgical management options available. The last decade has seen a rise in endoscopic bariatric interventions. These minimally invasive therapies can be used for patients who do not qualify or are unwilling to undergo bariatric surgery. Currently, there is limited formal training in bariatric endoscopy. In this commentary, we discuss our experience in establishing a center for bariatric endoscopy at a large academic medical center.

Keywords: Obesity, bariatric endoscopy, training, endoscopic sleeve gastropasty

INTRODUCTION

As the prevalence and global burden of obesity continue to rise worldwide, there is a growing need for evidence-based interventions to address this issue^[1]. There are a multitude of adverse health consequences associated with obesity, such as hypertension, diabetes mellitus, dyslipidemia, hepatic steatosis, some cancers, and an all-cause cardiovascular mortality^[2]. The economic burden of obesity is estimated to cost approximately two trillion dollars annually^[3].

The mainstay of obesity treatment includes lifestyle modifications, pharmacotherapy, and bariatric surgery. While pharmacologic therapy has demonstrated 5% to 10% weight loss compared to placebo, these effects are relatively modest and tend to be short-lived. Although bariatric surgery has been shown to be effective in achieving long-term weight loss, in countries following National Institute of Health criteria, it is



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Table 1. Summary of early lessons in assembling a bariatric endoscopy center

Institutional financial backing of the bariatric center
Multidisciplinary team effort including gastroenterologist, bariatric surgeons, gastrointestinal radiologists, nurses, behavioral psychologists as well as registered dietitians
Robust endoscopic training in numerous endoscopic techniques with surgical backup on hand
Minimize barriers for short and long term follow up for procedural complications

currently reserved for patients with a BMI of 40 or greater or those with a BMI of 35 or greater with obesity associated comorbid conditions. Only 1% of morbidly obese individuals undergo bariatric surgery^[4]. Some factors related to this include patients fear of complications, financial constraints, and long term post-bariatric surgery syndromes^[5].

Over the past decade, this has paved the way for numerous innovations in endoscopic bariatric therapies. These non-surgical therapies include intragastric balloons, endoscopic sleeve gastropasty, gastrointestinal bypass sleeves and aspiration devices as well as other novel devices^[6]. These minimally invasive therapies can be used for patients who do not qualify or are unwilling to undergo bariatric surgery. Currently, there is extremely limited formal training in bariatric endoscopy. In this commentary, we discuss our experience in establishing a center for bariatric endoscopy at a large academic medical center.

STARTING A PROGRAM

Training and team

Creating an effective endo-bariatric center requires a truly interdisciplinary team effort [Table 1]. This multidisciplinary team includes bariatric endoscopists (gastroenterologists in our center), bariatric surgeons, gastrointestinal radiologists, nurses, behavioral psychologists as well as registered dietitians^[7]. This team should have a comprehensive understanding of the pathophysiology of obesity in addition to the mastery of endoluminal device and procedure specific knowledge with respect to the mechanism of action and possible complications. A comprehensive and cohesive team allows for the successful utilization of the different endoluminal therapies that may be appropriate for different patient sub-populations in achieving long term weight loss. This is also helpful in the minimization and effective troubleshooting of post-procedural complications that may arise.

While many endoscopic bariatric therapies are extensions of the current endoscopic skills gastroenterologist use daily, a bariatric endoscopist should ideally be trained in many complex endoscopic techniques including endoscopic suturing and luminal stenting. At our program we provide a strong foundation and incorporate formal didactic lectures on primary obesity therapy management [i.e., intragastric balloon (IGB), endoscopic sleeve gastropasty (ESG)] as well as managing complications of bariatric surgery and weight regain (transoral outlet revision). We also require a minimum of 10 h of wet lab training followed by exposure to basic uses of endoscopic suturing (defect closure, stent fixation, fistula closure) of > 5 in number prior to assisting on their first ESG. Observing several ESG cases prior to trainees assisting with a hands-on role is also critical. We additionally believe that the first independent 5 ESG cases be proctored. While we do not have a set number of procedures trainees are required to complete, at present they are exposed to approximately over 400 ERCP and 400 EUS procedures per year. Lastly, to help with the implementation of bariatric endoscopy in clinical practice the American Society for Gastrointestinal Endoscopy (ASGE)^[8] has published a position paper to help provide guidance on the effective utilization of these therapies in clinical practice. It is important to recognize that this is just based on our early experience, and training in bariatric endoscopy can vary at each institution, depending on the endoscopist's and center's experience in training in bariatric endoscopy.

Equipment

Prior to starting a bariatric endoscopy program, it is essential to have all equipment that may be needed. A successful bariatric endoscopy program should offer patients multiple treatment options. These include

intra-gastric balloons, endoscopic sleeve gastropasty (ESG) procedure as well as the ability to manage post-bariatric surgery complications.

The endoscopic IGB was first proposed in the 1980s^[9]. The most used IGB is the Orbera IGB system (Apollo Endosurgery, Inc., Austin, TX, USA). ESG is the most offered endoscopic irreversible bariatric procedure. This procedure is performed with the use of an endoscopic suture system. The most widely used and available system is the OverStitch system (Apollo Endosurgery, Inc., Austin, TX, USA). The POSE procedure requires the incisionless operating platform (USGI Medical, Inc., San Clemente, CA, USA) for performing the procedure. We suggest that it is essential to have the commitment of the division and institutional leadership to provide financial support to have all available equipment prior to starting a bariatric endoscopy program.

Process of setting up a team and patient recruitment

Optimal patient selection is crucial in optimizing clinical outcomes. Patients that are referred to our center are usually BMI > 30 patients that are not candidates for bariatric surgery or a looking for minimally invasive procedures due to fear of surgical complications or long term post-bariatric surgery syndromes. All patients meet with our multidisciplinary team and undergo a comprehensive evaluation and education regarding the different endoluminal therapies available tailoring for the patient's ultimate goals. Lastly, meeting with a dietitian before and after the procedure is crucial in educating patients of the long lifestyle changes required to make durable long-lasting changes. Our program offers monthly nursing and dietitian visits as part of our comprehensive 1-year care program. Establishing a self-pay price from a large institution can take time and best to begin these conversations early with the administration with value analysis planning. Lastly, given the need for more long-term data in patients underwent bariatric and metabolic endoscopy, we also suggest developing infrastructure to carry out research studies.

TYPES OF PROGRAMS

Academic medical center vs. community practice

While a majority of the new bariatric and metabolic endoscopy therapies are being performed at large tertiary referral academic medical centers, there has been a growing amount of these procedures being performed in smaller community hospitals. Not only are some of these procedures technically feasible in the outpatient setting such as endoscopic sleeve gastropasty with similar procedure times, they also have parallel clinical outcomes with respect to percentage of total and excess body weight loss^[10]. While the clinical outcomes are similar, some challenges that community gastroenterologist will encounter in its widespread implementation is the reluctance on the part of payors to cover new procedures mentioned above as well as the infrastructure required. As the field of bariatric endoscopy continues to evolve and more studies show durable clinical outcomes with favorable safety profiles, we will see increased adoption of these procedures in the outpatient setting.

Training of the endoscopist

Given that there are limited formal bariatric endoscopy training programs available, the training of endoscopist can be challenging^[11]. To undertake bariatric endoscopy as an integral part of your practice, needs long-term commitment by the endoscopist and self-driven training. Prior to performing the first case in a human, it is advisable to practice on mechanical and *ex-vivo* simulators. Animal laboratories can often be set-up with the help of companies manufacturing endoscopic bariatric devices^[10]. In addition, there are several courses sponsored by gastroenterological organizations such as the ASGE. After basic understanding of bariatric endoscopic procedures and post-bariatric surgery anatomy is obtained, we suggest in-person shadowing at a high-volume bariatric endoscopy center. This includes shadowing the bariatric endoscopist in the office as well as during endoscopy. This allows first-hand experience of observing intra-procedural challenges and trouble shooting. In addition, for programs starting their bariatric endoscopy training

program, it is important to ensure that nurses or assistants (endoscopy technicians) undergo a robust training session on the use of bariatric endoscopy devices. We suggest developing a pre, intra and post procedural checklist to ensure the procedures go smoothly for beginning bariatric endoscopists. When the first case is being performed, it is essential to disclose this fully to the patient. In regard to preparation for the first in-human ESG for the endoscopist, it is advisable for the endoscopist to have no other cases for that day. The schedule should be fully blocked for this case. The endoscopist should have no other clinical responsibilities such as being on-call or covering the inpatient procedures. This way the endoscopist is completely focused on this procedure alone. Discussion should be done in advance with the endoscopy team as well as anesthesia, and expectations clearly laid out that given that this will be the first procedure of the endoscopist, it could take more time. The bariatric surgery team should be available for back-up in case of any complication. Proctoring from expert clinicians is highly recommended for the first several ESG cases and beyond those given a lengthy learning curve, ongoing industry presence during ESG cases is essential. These efforts ensure that the procedure will be carried as safely as possible.

CONCLUSION

As bariatric endoscopy gains market traction, more formal training will become widely available. However, in the interim as new programs continue to develop, it is important to have a multidisciplinary approach in treating obesity. All stakeholders involved should be on board prior to starting a bariatric endoscopy program. The bariatric endoscopist should be adequately trained in not only performing basic bariatric endoscopic procedures but should be adept in managing post bariatric surgery complications.

DECLARATIONS

Authors' contributions

Conceived, drafted, edited and revised the manuscript: Mlabasati J, Bilal M, Cohen J

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All authors declared that there are no conflicts of interest.

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Review

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Stereotactic radiotherapy for early-stage non-small cell lung cancer

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Abstract

Surgical resection is treatment of choice for early stage non-small cell lung cancer, even though 20%-30% of patients do not undergo surgery. Compared to conventional fractionated radiotherapy, stereotactic body radiotherapy (SBRT) has demonstrated excellent local control (LC) and overall survival (OS). Central and ultra-central lesions present higher toxicity rates after SBRT because of their proximity to mediastinal structures. Dose escalation studies have documented that 10-12 Gy per fraction is the maximal tolerable dose with acceptable rates of treatment adverse events and survival. Peripheral lesions can be safely treated with high radiotherapy dose (biologically equivalent dose of ≥ 150 Gy) and a different SBRT dose schedule has showed comparable results with LC rates $> 90\%$ and OS comparable to surgical resection. Elderly patients, defined as 75 years or older, are a subgroup of patients who may benefit the most from SBRT, as they have higher morbidity and mortality risks because of comorbidities and decreased lung function. At present, there are no randomized studies comparing SBRT with surgery for patients who are potential candidates for surgical removal. Retrospective studies and systematic reviews have showed encouraging results in terms of cancer-specific survival and LC.

Keywords: SBRT, ablative radiotherapy, early stage non-small cell lung cancer, NSCLC

INTRODUCTION

International guidelines suggest that the cornerstone of treatment for early stage non-small cell lung cancer (NSCLC) is surgical resection, with precise lobectomy and systematic mediastinal/hilar lymph node dissection the standard of care. Nevertheless, roughly 20%-30% of patients with stage I NSCLC do not undergo surgery^[1]. The 5-year cancer specific survival (CSS) rate for early-stage lung cancer patients who do not receive any treatment is around 16%^[2]. All patients need to be discussed at a multidisciplinary



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tumor board meeting involving the thoracic surgeon, lung specialist, clinical and radiation oncologist, radiologist, nuclear medicine physician and pathologist. Together, they will define the operability of the case and discuss the best treatment options. Currently, national and international guidelines purpose definitive radiotherapy as an alternative in the event patients are not candidates for surgery or if they refuse resection^[3,4]. Historically, studies have demonstrated that the local control (LC) rate with conventional radiotherapy was inadequate compared to surgery. Dose escalation studies have found that LC and survival were improved with doses ≥ 80 Gy. Thus, several accelerated radiotherapy regimens have been tested to achieve better results in terms of outcomes and toxicity. Limiting the dose to the surrounding tissues is an important goal, particularly because early stage NSCLC patients who are not suitable for surgery, are usually fragile due to age or other comorbidities. The stereotactic body radiotherapy (SBRT) technique has been developed for the treatment of localized lung lesions because it is a highly conformal and focused ablative treatment delivered precisely to a delineated target volume over a short period. Literature data have also demonstrated that the LC rate after SBRT ranges around 85%-100%^[5]. The SPACE trial^[6] was the first clinical trial to compare the outcomes of SBRT vs. conventional fractionated radiotherapy: it randomized 102 patients to receive 66 Gy of SBRT over three fractions or 3D conformal radiotherapy of 70 Gy over 35 fractions. It demonstrated non-inferiority of SBRT with no difference in progression free survival (PFS) and overall survival (OS) among groups with a comparable toxicity profile. Recently, the CHISEL trial^[7] proved that SBRT had a favorable toxicity profile and achieved superior LC compared to conventional radiotherapy: the 2-year LC rates were 89% vs. 65%, respectively. Thus, SBRT is considered the treatment of choice for patients with early stage NSCLC who are not candidates for surgery and it has seen widespread uptake in clinical practice. Despite rapid and wide adoption of SBRT, there still exists substantial variation in patient selection, staging, radiotherapy technique (planning and delivery), the prescribed dose and dose per fraction, duration and modality of follow-up. This paper aims to review the main questions regarding the use of SBRT in clinical practice, by reviewing the most important data published so far. We discuss the maximum tolerable dose of SBRT, toxicity, LC and OS outcomes for peripheral, central and ultra-central lesions, and we investigate its effectiveness and tolerability in the elderly subpopulation. Finally, we review the most relevant data comparing SBRT with surgery.

Peripheral lesions

A peripheral lesion is defined as a non-central lesion: it includes all tumors arising from the lung parenchyma at least 2 cm from the principal bronchial tree. Several dose escalations studies have demonstrated that LC is improved by delivering a higher biological effective dose (BED) to the target. The main stone study published by Onishi *et al.*^[8] reported that LC highly correlates with radiation dose. The authors documented that the 5-year LC was statistically and significantly higher (91.6% vs. 57.1%) in the group of patients treated with a BED ≥ 100 Gy compared to those treated with less than 100 Gy (assuming lung cancer $\alpha/\beta = 10$). These observations were confirmed by subsequent prospective studies. In the series published by researchers from Washington University, it was found that higher maximum doses led to higher rates of local tumor control. Moreover, on multivariate analysis, only maximum tumor doses correlated with tumor control^[9].

Patients with peripheral lesions had an excellent outcome after SBRT as the 2-year LC and OS rates were 95% and 57.6%, respectively. Patients with peripheral lesions tolerate larger doses per fraction, even in those considered unfit for surgery because of comorbidities and poor lung function [Table 1].

The rate of 2-year toxicity-free interval, after SBRT dose of 60-66 Gy/3 fractions (20-22 Gy per fraction) given over a period of 1.5-2 weeks, was significantly higher in patients with peripheral lesions compared to central lesions at 83% and 54%, respectively^[10]. No treatment-related deaths were observed for high dose SBRT (BED 150 Gy) in the Radiation Therapy Oncology Group (RTOG) 0236 trial, and the Grade 3-4 toxicity rate was 27.2%. The RTOG 0236 trial involved 59 patients with peripheral T1-2 (< 5 cm) NSCLC

Table 1. Peripheral lesion

Study	Fractionation	Toxicity (incidence of adverse events)	Survival rates
Timmerman <i>et al.</i> ^[10] (RTOG 0236)	60-66 Gy/3 fr	Grade 3-5: 20%	2-year LC: 95% 2-year OS: 54.7%
Timmerman <i>et al.</i> ^[11] (RTOG 0618)	54 Gy/3 fr	Grade 3: 12.7% Grade 4: 3.6% No Grade 5 toxicity	3-year LC: 97.6% 3-year OS: 55.8%
Guckenberger <i>et al.</i> ^[14]	45 Gy/3 fr 48 Gy/4 fr 54 Gy/3 fr		LC around 90% LC around 90%
Videtic <i>et al.</i> ^[15] (RTOG 0915)	34 Gy/1 fr 48 Gy/4 fr	Toxicity: 16% Toxicity: 12%	2-year OS: 61.3% 2-year OS: 77.7%
Singh <i>et al.</i> ^[16]	30 Gy/1 fr 60 Gy/3 fr	Thoracic Grade 3: 16% No Grade 4-5 Thoracic Grade 3: 12% No Grade 4-5	2-year LC: 94.9% 2-year OS: 73% 2-year LC: 97.1% 2-year OS: 62%
Cummings <i>et al.</i> ^[18]	30 Gy/1 fr 50 Gy/5 fr	Grade 3 (lung toxicity): 4.6% Grade 3 (lung toxicity): 7.1%	1 and 2-year LC: 95%-88% 1 and 2-year OS: 84%-61% 5-year OS: 17% 1 and 2-year LC: 93% -90% 1 and 2-year OS: 85% -70% 5-year OS: 39%
Stephans <i>et al.</i> ^[19]	54 Gy/3 fr 30-34 Gy/1 fr 48-50 Gy/4-5fr	Lung toxicity: 5.1% Chest wall toxicity: 23.7% Lung toxicity: 3.2% Chest wall toxicity: 8.6% Lung toxicity: 3.8% Chest wall toxicity: 7.7%	2-year LF: 13.1% 2-year LF: 21% 2-year LF: 15.5%

Fr: fraction; LC: local control; OS: overall survival; LF: local failure

lesions who were not candidates for surgery (unsatisfactory lung function tests: forced expiratory volume in 1 sec -FEV1- < 40%), and received 54 Gy/3 fractions of SBRT over 1.5-2 weeks. After a median follow-up of 34.4 months, the estimated 3-year LC and OS were 97.6% and 55.8%, respectively^[11].

Patient selection can make the difference in toxicity and survival data: healthier patients reported less toxicity, better local control and were able to tolerate treatment (total dose delivered and dose per fraction). The RTOG 0618 trial enrolled patients with T1-2 (< 5 cm) tumors that were potentially operable (the median FEV1 72.5%, range: 38%-136%) to receive 54 Gy/3 fractions (18 Gy each fraction) of SBRT over 1.5-2 weeks. After a median follow-up of 48.1 months, 2-year LC was 96% and 4-year OS was 56%, no Grade 4-5 toxicity was registered, and the incidence of Grade 3 toxicity was 15%^[12]. LC was excellent: the 3- and 5-year LC rates were 96% and 93%, respectively, for fit patients who refused surgery. The SBRT dose was 60 Gy/5 fractions (12 Gy per fraction) for peripheral lesions not adjacent to the chest wall, and 50 Gy/5 fractions (10 Gy per fraction) for peripheral lesions or close to the chest wall^[13]. The Advisory Committee on Radiation Oncology Practice (ACROP) consensus conference^[14] suggested that patients who are not candidates for surgery might benefit from PTV minimum doses ranging from 105 Gy to 113 Gy. Consequently, the recommended fractionations were 45 Gy/3 fractions (15 Gy per fraction) for peripherally located lesions (> 1 cm from chest wall) and 48 Gy/4 fractions (12 Gy per fraction) for lesions having broad chest wall contact. This regimen can achieve a 90% local control rate and has an acceptable toxicity profile. The consensus conference also suggested considering 54 Gy/3 fractions (18 Gy per fraction) as the maximum tolerable dose for patients who refused surgery, without severe comorbidities and have favorable long-term life expectancies.

The RTOG 0915/North Central Cancer Treatment Group N0927 was a randomized phase II trial designed to evaluate toxicity related to two regimens for peripheral lesions: 34 Gy in a single fraction and 48 Gy in four consecutive daily fractions. Grade 3 toxicity rates at 1 year after treatment was similar among groups.

In particular, the authors found no difference in chest wall severe adverse events. Compared to RTOG 0236, the rate of toxicity was lower and outcome results were comparable as the 2-year OS rate was 61.3% in 34 Gy/1 fraction schedule and 77.7% in fractionated SBRT, respectively^[15]. No significant difference in LC, OS, adverse events and lung function in patients treated with 30 Gy in a single fraction vs. 60 Gy/3 fractions (20 Gy per fraction) was reported. Toxicity rate was 16% in the single fraction arm vs. 12% in the multi-fractions regimen^[16]. Retrospective propensity-matched comparison between the 3 fractions regimen (total dose 60 Gy, 20 Gy per fraction) and the 5 fractions schedule (total dose 50 Gy, 10 Gy per fraction), showed no significant differences in OS, PFS, local failure and distant relapse at 2 years^[17]. No significant conclusions about optimal dose fractionation in peripheral lesions can be derived so far. Both single and multi-fraction SBRT produce comparable outcomes and limited adverse events. The 1- and 2-year LC rate ranged between 93%-95% and 88%-90% in patients treated with single fraction SBRT (30 Gy/1 fraction) over a fractionated regimen (50 Gy/5 fractions: 10 Gy per fraction). OS was significantly longer in patients treated with fractionated SBRT (1- and 2-year OS rates were 84% and 61% with one fraction group vs. 85% and 70% in the fractionated schedule, $P = 0.01$), unless the baseline tumor size was imbalanced across groups and the fractionated schedule cohort presented a larger treatment volume^[18]. Results of a large single institution series suggested that 54 Gy/3 fractions (18 Gy per fraction) of SBRT led to improved LC compared to 30-34 Gy/single fraction and 48-50 Gy/4-5 fractions (10-12 Gy per fraction). The lung toxicity rate (any Grade) was slightly higher with the 3 fractions schedule at 5.1% vs. 3.2% and 3.8% in the single and 4-5 fractions schedule, respectively. Moreover, chest wall toxicity was more common in the 3 fractions (23.7%) compared to 8.6% and 7.7% in the single and 4-5 fractions schedule, respectively^[19].

Central and ultra-central lesions

Central lesions

Currently, lung tumors located around the proximal bronchial tree are defined as “Central”. This refers to the zone 2 cm distal to the trachea, carina, and major lobar bronchi up to their first bifurcation. Patients treated for central lesions were more likely to experience treatment related side effects, as demonstrated by a phase II trial, which enrolled NSCLC patients who were clinically staged as T1-3 (< 7 cm), not candidates for surgery, and received 60-66 Gy/3 fractions (20-22 Gy each fraction) of SBRT. The authors reported that the peri-hilar/peri-central tumor location was a stronger predictor of toxicity in both uni- and multi-variate analyses ($P = 0.004$)^[10]. Medically inoperable patients with central lesions were recruited in a prospective phase I/II trial to investigate the toxicity and efficacy of four dose levels (from 9 to 12 Gy per fraction), measured as an objective 2-year LC rate > 80%. They defined all lesions located within 2 cm around the proximal bronchial tree, or 5 mm by the mediastinal pleura or parietal pericardium as central. The reported acute Grade 3-4 toxicity rate was 6%, while 27% developed late Grade 3 toxicity and 16% had grade 4-5 late adverse events^[20]. Thereafter, a phase I-II dose-escalation study (RTOG 0813) was designed to determine the maximum tolerable dose for central tumors. Patients were assigned to receive SBRT in a 5 fractions schedule, with each dose per fraction ranging from 10-12 Gy; dose limiting toxicity was defined as any Grade ≥ 3 adverse event that occurred in the first year after treatment. The maximum tolerable dose was 12 Gy per fraction (total dose 60 Gy) which reported 7.2% Grade ≥ 3 toxicity^[21].

Several studies have investigated the optimal dose of treatment for centrally located lesions by balancing survival outcomes and toxicity. SBRT for patients with central tumors achieved markedly better local control compared to conventional radiotherapy. A prospective, phase II trial investigated an alternative treatment schedule to the 60 Gy/3 fractions scheme, which is not recommended in central lesions due to its high toxicity rate. Patients who were medically inoperable were treated with 55 Gy/5 fractions (11 Gy per fraction) of SBRT achieved an estimated 2-year LC and OS of 85% and 43%, respectively. With a 2-year local control rate > 80%, the phase II trial achieved its primary end point after a median follow up of 17 months. Most of the tumors were located centrally (84%), within 2 cm of the proximal bronchial tree; 16% were located within 5 mm of the mediastinal or pericardial pleura (ultra-central lesions)^[20]. The

Table 2. Central lesion

Study	Fractionation	Toxicity (incidence of adverse events)	Survival rates
Roach <i>et al.</i> ^[20]	55 Gy/5 fr	Acute Grade 3-4: 6% Late Grade 3: 27% Late Grade 4-5: 16%	2-year LC: 85% 2-year OS: 43%
Bezjak <i>et al.</i> ^[21] (RTOG 0813)	60 Gy/5 fr	Grade ≥ 3: 7.1%	2-year LC: 87.9% 2-year OS: 72.7%
Ultra-central lesion Tekatli <i>et al.</i> ^[22]	60 Gy/12fr	Grade 3: 38% Possible treatment related death: 21%	Median OS: 15.9 months 3-year OS: 20.1%
Zhao <i>et al.</i> ^[23]	60 Gy/8 fr	Grade 3: 5.1% No Grade 4-5.	1 and 3-year LC: 98% & 84%

Fr: fraction; LC: local control; OS: overall survival

RTOG 0813 Phase II trial indicated that 12 Gy per fraction was the maximum tolerable dose for medically inoperable patients with centrally located, early stage tumors. Outcome results were comparable with the results of patients treated for peripheral lesions. Seventy-one patients who were not fit for surgery, mostly elderly and with comorbidities, were recruited to receive SBRT of 60 Gy delivered in 5 fractions (12 Gy per fraction) *vs.* 57.5 Gy/5 fractions (11.5 Gy per fraction), and 65% of cancers were staged as T1. The 2-year LC rate was 87.9% in the 12 Gy per fraction cohort *vs.* 89.4% for the 11.5 Gy per fraction, and the 2-year OS rate was 72.7% (12 Gy) *vs.* 67.9% (11 Gy)^[21] [Table 2].

Ultra-central lesions

“Ultra-central” lesions are defined as tumors with planning target volume (PTV) that mostly overlaps the mediastinal space. A retrospective study evaluated if ultra-central lesions were at higher risk for developing toxicity. Forty-seven ultra-central lesions were treated with 60 Gy/12 fractions (5 Gy each fraction) of SBRT with a median total PTV of 104.5 cm³ (range 17.7-508.5), and the tumor diameter exceeded 5 cm in 60% of patients. They reported a 38% rate of Grade 3 toxicity and a 21% rate of “possible” and “likely” treatment-related death, including 15% of fatal pulmonary hemorrhage^[22].

In clinical practice, mediastinal organs at risk have resulted in compromising PTV coverage in SBRT treatment of ultra-central lesions. A retrospective study reviewed 98 patients with central and ultra-central lesions treated with 60 Gy/8 fractions (7.5 Gy per fraction) of SBRT. Outcomes for the subgroup of patients with ultra-central lesions were compared to the group of patients with central lesions whose PTV did not cover mediastinal structures: no difference in beneficial outcomes as well as adverse events were registered. The median PTV volume was 25.7 cc (range 5.1-134.5 cc) for central lesions and 42.1 cc (range 6.6-184.8 cc) for ultra-central. After a median follow-up of 22.9 months, LC rates at 1- and 2-years were 97.8 and 93.7%. On multi-variate analysis, the internal target volume (ITV) was a prognostic factor for local control ($P = 0.001$). Generally, the cumulative incidence of Grade 3 toxicity was low (5.1%) and no severe esophageal or cardiac toxicity was registered^[23] [Table 2].

Due to the very high toxicity rates reported, we do not recommend SBRT as an option in patients affected by early-stage NSCLC when the target volume overlaps mediastinal structures.

Elderly population

Elderly patients, defined as 75 years old or older, are a subgroup of patients who may benefit from SBRT due to higher morbidity and mortality risks related to surgery because of comorbidities and decreased lung function. 62,213 early stage NSCLC patients older than 60 were reviewed using the Surveillance, Epidemiology and End Results database. Data suggested that surgery declined sharply from being the treatment of choice in 81% of patients in the 60-64 years old group to only 21% of patients older than 90 years^[24]. Compared to historical outcomes for surgery in the elderly, SBRT is considered to show similar

survival even though its toxicity rate is well below that of morbidity rates after surgery. Outcomes of 772 early stage NSCLC patients treated with 50 Gy/4 fractions (12.5 Gy per fraction) of SBRT, or in cases of central lesions, 70 Gy/10 fractions (7 Gy per fraction), were analyzed to verify safety in the elderly population. It was found that the elderly group had no significant difference in PFS, OS and toxicity compared to the patients younger than 75. After a median follow-up of 55 months, the cumulative incidence of loco-regional failure was 17.3%. The 1-, 3- and 5-year OS rates for patients ≥ 75 years were 86%, 57.5% and 39.5%, respectively. No Grade 4-5 toxicity was registered, and Grade 3 toxicity rate was comparable (ranging around 1-2%): the group of patients older than 75 did not differ from others^[25]. SBRT can thus be very safely and effectively utilized in patients older than 80 for Stage I tumors at a median ablative dose (BED ≥ 100 Gy) of 54 Gy/3 fractions (18 Gy per fraction) with 1- and 2-year LC rate of 100% and 92.3%, and no reported toxicity Grade 2-5^[26]. An observational study reviewed 58 consecutive patients ≥ 80 years who received SBRT for early-stage NSCLC. Overall, the 3-year OS rate was 56.4%, suggesting the efficacy of SBRT; patients with Karnofsky performance status ≥ 75 had improved 3-year CSS and OS rates (99.4% and 91.9%, compared to 47.8% and 23.6% in patients with KPS < 75 , respectively)^[27].

Oncological outcomes and toxicity rates were analyzed in NSCLC Stage I patients older than 90 years and treated with SBRT at a dose of 50 Gy/5 fractions daily (10 Gy per fraction). Nineteen patients were identified: the median age was 91.6 years, the median tumor size was 2.1 cm, and 31.6% were central lesions. Two-year rates of local failure and OS were 5.6%, and 47.8%; no Grade 3 toxicity was registered^[28].

SBRT vs. surgery

SBRT is a noninvasive, well-tolerated ablative treatment perceived as an attractive option even for patients who are potentially fit for surgery. For this reason, three randomized clinical trials (ROSEL, STARS, ACOSOG Z4099) have been launched to compare SBRT with lobectomy in patients deemed medically operable. Each of this trial has been closed prematurely because of scarce accrual of results, although a pooled analysis of the ROSEL and STARS trials reported reduced morbidity and no inferior OS and PFS of SBRT compared to lobectomy. The estimated 3-year OS rate was 95% for SBRT vs. 79% in the surgical group (HR = 0.14, 95%CI: 0.017-1.19). It must be emphasized that the small sample size is such that this data not reliable^[29]. Retrospective studies reported comparisons amongst similar groups of patients treated with surgery or SBRT, even though most authors reported unmatched baseline characteristics. Patients treated with surgery were more likely to be fit, younger, healthier, and have more favorable lung function; on the other hand, the SBRT group proportionally had more T1 tumors.

According to the American Society of Clinical Oncologists^[30], for patients with standard operative risk (1.5% mortality rate) and Stage I NSCLC, SBRT is not recommended as an alternative to surgery outside clinical trials. The standard operative risk reached 4.4% in patients aged 81 years or more, even though age, sex, cardiovascular and pulmonary comorbidities, and patients' functional status are factors influencing peri-operative risk.

SBRT vs. lobar resection

Lobectomy represents the standard of care for early stage lung cancer with 3- and 5-years OS rate of approximately 82% and 66%, respectively. The minimally invasive approach (video-assisted thoracoscopic surgery) has showed non-inferior results in survival and fewer peri-operative complications and morbidity compared to open lobectomy^[31]. In the absence of clinical trials, more reliable data has come from a meta-analysis of propensity score-matched analysis comparing lobectomy to SBRT. OS rate at 1 year was similar among groups, but data favored surgery at 3 years. Nevertheless, CSS rates were comparable in both arms, which indicates that SBRT patients may be less healthy and die of non-cancer causes^[32]. A systematic review investigated the efficacy of both SBRT and lobectomy for Stage I-II disease and found no difference in 1-year survival rate. However, long-term results indicate a benefit of lobectomy over SBRT: lobectomy

significantly improved 3-year OS (OR = 2.11, 95%CI: 1.55-2.86) and 5-year OS (OR = 2.40, 95%CI: 1.71-3.36), 3-year CSS (OR = 1.94, 95%CI: 1.05-3.57) and 3 year PFS (OR = 1.63, 95%CI: 1.12-2.36)^[33].

Many observational studies suggest that the survival advantages reported from lobectomy could have been a consequence of treatment selection criteria. Data on patients deemed fit for surgery but treated with SBRT have suggested that OS (HR = 1.68, 95%CI: 0.72-3.90) and PFS (HR = 0.61, $P = 0.09$) were comparable to that from surgery. Performance status was also found to impact significantly on OS^[34]. The pattern of failure studied in a t-matched comparison study was similar between patients who underwent an optimal surgical operation and those who received SBRT. There was a trend of a distant-recurrence free interval in favor of lobectomy because of reported occult nodal involvement. Nodal metastases have been detected in 20% of patients treated with surgery and almost 15% received adjuvant systemic therapy (pN2). Surgical patients had higher OS rate (63.5% vs. 29.6%, $P < 0.0001$) with no difference in CSS. The rate of complete response was similar, whereas the 4-year LC rate was significantly higher in resected patients (98.7% vs. 93.6% $P = 0.015$)^[35]. Surgery had a 1 in 6 chance of discovering occult nodal metastasis, while only 1 in 9 would benefit from adjuvant chemotherapy. Adjuvant chemotherapy improved OS in patients with nodal involvement, but surgery (either lobectomy or sub-lobar resection) was related with severe adverse events and mortality rate. A meta-analysis confirmed that patients who underwent surgery had better OS over SBRT [HR = 1.48, (95%CI: 1.26-1.72), $P < 0.001$, $I^2 = 80.5\%$] but there was no difference in lung cancer-specific survival^[36]. Lobectomy demonstrated survival advantages over SBRT even when data analysis had been restricted by exclusion of older patients, poor performance status and clinical stage IB. A meta-analysis noted that SBRT treatment was delayed compared to surgery. A possible explanation is that patients who are not candidates for surgery may require repeat CT scans in order to demonstrate increase of the unbiopsied nodule's size^[37]. Surgery (lobectomy and sub-lobar-resection) showed statistically superior outcomes for OS, CSS, PFS and loco-regional control compared to SBRT in both matched and un-matched cohorts for mid- and long-term outcomes. Distant control was not statistically improved by surgery but there was a trend suggesting lobectomy could show an advantage in the long term. The extent of favorable long-term outcomes in surgery may be influenced however, by imbalances in baseline patient characteristics, preoperative comorbidities or tumor characteristics^[38].

SBRT vs. limited resection

Detection of early stage lung cancer is increasing due to the development of diagnostic imaging, and clinicians have to face difficult treatment decisions, particularly in older patients with comorbidities and poor lung function. Less invasive procedures such as SBRT and limited lung resection (wedge, segmentectomy) provide a good alternative because they are better tolerated and have fewer adverse events. Segmentectomy is an anatomic lung resection in which interlobar and parenchymal nodes are identified and removed for pathology; wedge resection is a non-anatomic resection without nodal sampling. SBRT and wedge resections have similar survival outcomes, while the OS and CSS rates supported segmentectomy over SBRT, probably due to patient characteristics. Lung adverse events were reported more frequently after surgery (28% vs. 14%, $P < 0.001$)^[39]. Patients ineligible for lobectomy could be candidates for wedge resection or SBRT, unless SBRT patients have more comorbidities and are older; no statistical difference in loco-regional recurrence, distant metastasis, and PFS were observed between groups. In an unmatched cohort analysis, there was a trend towards decreased local recurrence in SBRT over wedge resection: 4% vs. 20% ($P = 0.07$). OS was also higher in the wedge resection arm (87% with surgery vs. 72% in SBRT, $P = 0.01$) but the CSS was equivalent (93% in SBRT vs. 94% with wedge). The authors suggested that the reduced OS in the SBRT arm could be related to both a higher rate of comorbidities before treatment, and complications and mortality rate post-treatment^[40]. Sub-lobar resection for Stage I NSCLC showed survival advantages over SBRT in a propensity-score matched analysis with 1-and 2-year OS rates of 92% and 82%. Moreover, even though segmental resection showed better OS vs. wedge resection, both of them have survival advantages over SBRT of a median dose of 30-66 Gy in 2-8 fractions. The 1-, 2-, 3- and 5-year

relative survival rates were 96%, 90%, 84% and 71% for sub-lobar resection compared to 93%, 78%, 65% and 46% respectively for SBRT^[41]. Moreover, a comparative analysis among patients Stage IA treated with SBRT or wedge resection found the SBRT cohort experienced lower survival compared to wedge resection: 5-year OS rate was 30% vs. 55.2% ($P < 0.001$) in unmatched analysis and still remained significantly in favor of surgery after adjustment for covariates (31% vs. 49.9%, $P < 0.001$)^[42].

CONCLUSION

Early stage non-small cell lung cancer patients have excellent 5-year survival rates of 60-80% if treated. The standard of care is lobectomy, but surgery is not always an option. SBRT delivers a high conformal ablative dose to the target, resulting in local control with an acceptable toxicity profile. Randomized clinical trials have tried to investigate SBRT for patients who are not candidates for surgical resection, and have showed encouraging results not inferior to surgery. Unfortunately, the trials designed for testing SBRT in patients who are potentially operable have been terminated for scarce accrual of results. Many systematic reviews and meta-analysis have tried to answer the question whether SBRT can be equal to surgery in fit patients, but results are not definitive. Therefore, SBRT is an effective and safe alternative for patients with Stage I-II NSCLC who are not candidates for surgery or who refuse surgical treatment.

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Authors' contributions

Conception and design, acquisition of data, analysis and interpretation of data: Reverberi C, Trovò M

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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Review

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Trends in the evolution to robot-assisted minimally invasive thoracoscopic esophagectomy

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Abstract

Much effort has been made to improve outcomes and/or minimize the invasiveness of esophagectomy for thoracic esophageal cancer. This has led to the evolution from open esophagectomy to thoracoscopic minimally invasive esophagectomy (MIE), and from MIE to robot-assisted minimally invasive esophagectomy (RAMIE). RAMIE is being applied clinically to overcome the limitations of MIE. In this article, we review the trends in the evolution from thoracoscopic MIE to RAMIE. It has now been demonstrated that RAMIE is both safe and feasible, and may decrease morbidity and mortality rates associated with esophagectomy and improve oncological outcomes. On the other hand, there are still many problems that need to be solved.

Keywords: Esophagectomy, esophageal cancer, robot-assisted esophagectomy, thoracoscopic esophagectomy

INTRODUCTION

Esophageal cancer is the 6th highest cause of cancer mortality worldwide due, in large part, to its high potential for metastasis^[1]. The most reliable curative treatment is surgery entailing radical resection of the esophagus with extended lymphadenectomy in the mediastinum, abdomen, and neck. However, esophagectomy is associated with high postoperative morbidity (about 40%) and mortality (about 3.4%)^[2,3]. To improve outcomes, patients are often treated with multimodal treatments such as neoadjuvant



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Table 1. RAMIE history

Year	
1960s	Start of development of a remote operation system
1998	DVSS enters clinical trials, first commercial sale
2000	DVSS obtains Food and Drug Administration clearance
2001	Performance of the first transatlantic surgery (robotic cholecystectomy)
2003	The first transhiatal RAMIE
2004	The first transthoracic RAMIE

DVSS: Da Vinci Surgical System; RAMIE: robot-assisted minimally invasive esophagectomy

chemotherapy or chemoradiotherapy, and there is much surgical effort towards improving operative techniques^[4,5]. This has led to the evolution from open esophagectomy (OE) to thoracoscopic minimally invasive esophagectomy (MIE)^[6], and from MIE to robot-assisted minimally invasive esophagectomy (RAMIE)^[7]. Despite the many advantages of MIE, there are several associated limitations. RAMIE, which has advantages in terms of an enhanced three-dimensional magnified view, tremorless action, and articulated instruments, is being applied clinically to overcome the limitations of MIE^[8]. In this article, we review the trends in the evolution from thoracoscopic esophagectomy to MIE and RAMIE.

HISTORY OF RAMIE

In the 1960s, the US Army and NASA began research on surgical robots with the aim of developing a remote operative system. It took nearly 30 years to complete the first fully functional surgical robot system. Called the Da Vinci Surgical System (DVSS), it has been clinically applied in the USA since 1997. In 1998, DVSS entered clinical trials and became commercially available in the USA. In 2000, DVSS was approved by the USA Food and Drug Administration. In 2001, a French surgeon, Jacques Marescaux, successfully performed the first transatlantic robotic-assisted cholecystectomy while working in the USA^[9]. In 2003, Talamini *et al.*^[10] reported the first series of transhiatal RAMIE. This was 8 years after the first transhiatal conventional MIE was reported by DePaula *et al.*^[11] in 1995. In 2004, Kernstine *et al.*^[12] reported the first series of transthoracic RAMIEs, which was 12 years after the first transthoracic conventional MIE was reported by Cuschieri *et al.*^[6] in 1992. Since then, RAMIE has been performed worldwide in many institutions. Moreover, given its many unique advantages, further clinical application of RAMIE is now being widely investigated. The history of RAMIE is summarized in Table 1.

CHARACTERISTICS OF THE OPERATIVE APPROACHES TO ESOPHAGECTOMY

MIE was introduced to improve outcomes and/or reduce the invasiveness of OE, and it has produced satisfactory results. In 2003, Luketich *et al.*^[13] reported the first large series of total MIEs and reported impressively low incidence of morbidity and mortality among 222 patients. Total MIE is performed by starting with a transthoracic MIE, followed by laparoscopic surgery to mobilize the stomach and perform upper abdominal lymphadenectomy. Transthoracic MIE provides improved magnified vision, less chest wall injury and relatively easy access to the upper thoracic structures, while laparoscopic surgery has less abdominal wall injury and less blood loss due to the pneumonic pressure. The first published randomized control trial in 2012, the TIME trial, is considered to be the cornerstone of MIE studies^[14]. Between 2009 and 2017, eight meta-analyses were published, comparing postoperative and oncologic outcomes of MIE and OE^[15]. MIE was generally found to be superior to OE in terms of intraoperative blood loss, acute immunological response, postoperative pulmonary infections, length of hospital stay, postoperative pain scores, and quality of life. Furthermore, the lymph node dissection (LND) yield and 3-year survival were equivalent^[14,16,17]. However, the two-dimension view, reduced eye-hand coordination, narrow operative field, restricted freedom of movement of operative instruments, moving targets, and nearby vital structures are all limitations such that MIE remains a highly complex procedure to be mastered by the surgeon^[8,18]. For example, the learning curve for an intrathoracic anastomosis was 119 cases when the incidence of

Table 2. Characteristics of each approach to esophagectomy

	OE	MIE	RAMIE
Difficulty level of technique	Relatively easy	Highly complex	Easier than MIE
Special points	Conventional operative method	Better vision	Zoomed-in enhanced three-dimensional vision
	with a lot of history	A two-dimensional view	Better overview
	Gold standard method	Reduced eye-hand coordination	Increased range of movement
		Restricted range of movement	Tremorless actions
			Flexible endo-wrists
Ergonomic conditions	Normal	Worst	Best
Blood loss	More	Less	Least
Operative time	Shorter	Longer	Longer
Postoperative pain score	High	Lower	Lower
Postoperative respiratory complications	More	Less	Less
Difficulty and exactness of upper mediastinum lymph node dissection	Difficult to access	More challenging maneuver than OE	Easier than MIE
	Equivalent	Equivalent	More exact
Postoperative recurrent laryngeal nerve paralysis	Equivalent	Equivalent	Reduced
Intrathoracic hand-sewn anastomosis	Difficult	The most difficult	Easy compared to MIE
Acute immunological response	More	Less	Same as total MIE
Functional recovery	Slowest	Fast	Same as total MIE
Length of hospital stay	Longest	Short	Same as total MIE
Mortality	Equivalent	Equivalent	Equivalent
Cost	Equivalent	Equivalent	Highest
Survival	Equivalent	Equivalent	Equivalent

OE: open esophagectomy; MIE: minimum invasive esophagectomy; RAMIE: robot-assisted minimally invasive esophagectomy

anastomotic leakage was the determining parameter (the anastomotic leakage rate dropped from 18.8% to 4.5%)^[18]. The learning phase of MIE was also considered to be a likely explanation for the higher re-operation rates as compared to OE in multiple population-based studies^[19-22]. This may explain the findings from a survey amongst esophageal surgeons in 2014, which showed that only 43% of the respondents reported MIE as their preferred approach^[23]. Indeed, due to its high technical complexity, MIE has not been adopted as the standard approach for esophageal cancer. These issues are summarized in Table 2.

A hybrid MIE (HMIE), which combines laparoscopy with a conventional thoracotomy, or combines a thoracoscopy with a conventional laparotomy, has been suggested as an alternative to total MIE^[24]. Messenger *et al.*^[25] reported that patients undergoing HMIE showed less mortality at both 30 (3.3% vs. 5.7%) and 90 days (6.9% vs. 10%) when compared to OE. In addition, Mariette *et al.*^[26] reported a randomized phase III trial (MIRO trial), which found that HMIE had a lower incidence of perioperative complications (36% vs. 64%), especially pulmonary complications (18% vs. 30%), with equivalent 3-year survival (67% vs. 55%) when compared to OE. Studies comparing HMIE with total MIE are scarce. In one study, however, Bonavina *et al.*^[27] compared a series of 80 total MIE versus 80 HMIE patients and found no differences in early postoperative complications or mortality. In addition, Grimminger *et al.*^[28] reported a series of 75 patients (HMIE 25, total MIE 25, RAMIE 25), which showed comparable morbidity and short-term outcomes in the three groups, although the total minimally invasive approaches appear to be associated with a lower incidence of complications such as pneumonia and wound infections. Those studies showed that although HMIE is a transitional operative method between OE and total MIE, because of its relatively lower difficulty level, somewhat reduced invasiveness and satisfactory clinical outcomes, it is a valuable operative method worth being performed.

To overcome the disadvantages of total MIE and HMIE, a robotic surgical system was developed and applied clinically. Transhiatal RAMIE was first introduced in 2003^[11], and transthoracic RAMIE

was introduced a year later^[12]. Although RAMIE is still under development, it is now described as a promising minimally invasive operative method with short-term and long-term clinical outcomes that are equivalent to (or perhaps better than) those achieved with OE and MIE [Table 2]^[29]. In a US report, 32.1% of esophageal cancer patients were treated with MIE. Of these, 19.6% were RAMIE^[30]. In that report, no differences in postoperative mortality or disease-free survival was noted between MIE and RAMIE^[30]. Nevertheless, given the many unique advantages of the robot, it is expected to decrease the morbidity and mortality rates of surgery for esophageal cancer and to improve oncological outcomes. Results of the recently published ROBOT trial showed improved clinical outcomes with reduced surgical and cardiopulmonary complication rates, reduced pain and improved functional outcomes with RAMIE as compared to OE^[31]. Moreover, RAMIE was associated with less intraoperative blood loss, lower postoperative pain scores, faster functional recovery, and better quality of life when compared to OE^[31]. Lymph node yield and overall survival did not differ between the two approaches, indicating that RAMIE offers short-term benefits while maintaining the high oncological standards. Needless to say, evidence remains weak due to limited RCT results, and more RCT studies are still needed.

Additionally, Yun *et al.*^[32] showed that RAMIE is also safe and feasible for use with patients who have received neoadjuvant chemoradiotherapy for locally advanced esophageal cancer, with postoperative mortality and morbidity rates comparable to that in OE. Another recently published study compared the clinical benefits of RAMIE with conventional OE. They showed that RAMIE could be a better surgical option for selected esophageal squamous cell carcinoma patients, offering both short-term and long-term benefits^[33]. Although both the short-term and long-term outcomes of RAMIE appear equivalent to MIE in most studies, one paper showed that RAMIE for esophageal cancer patients with node-positive disease in the superior mediastinum is associated with increased mortality (7.5%) and morbidity^[34].

LYMPH NODE DISSECTION IN RAMIE

The number of lymph nodes removed is a key factor contributing to the improved survival of esophageal cancer patients^[35]. LND along the recurrent laryngeal nerve (RLN) is considered beneficial; however, RLN LND is frequently complicated by RLN palsy (20%-80%), which is especially common on the left side. Early meta-analysis studies showed that, unfortunately, MIE does not reduce the rates of postoperative RLN palsy following RLN LND^[36-38]. On the other hand, RAMIE has several advantages for LND, especially RLN LND [Table 2]. The ROBOT trial showed that a mean of 27 and 25 lymph nodes were harvested in RAMIE and OE, respectively (not significantly different)^[31], which demonstrated that robotic surgery is at least comparable to open surgery for retrieving a sufficient number of lymph nodes. Although most early studies have found that the lymph node yield with RAMIE and MIE are similar^[39-41], in two recent series in which RAMIE and MIE were applied to upper mediastinal LND, markedly larger numbers of lymph nodes were harvested with RAMIE (median 37-49 vs. 19-21)^[42,43]. In addition, when Motoyama *et al.*^[44] compared the number of lymph nodes dissected from around the left RLN, they found that significantly more lymph nodes were dissected with RAMIE than MIE (median 6 vs. 4). This indicates that a robot-assisted surgical system may enable more extensive dissection of lymph nodes around the left RLN. Similarly, Park *et al.*^[42] demonstrated that the total number of dissected lymph nodes was significantly greater in the RAMIE group (37.3 ± 17.1 vs. 28.7 ± 11.8 ; $P = 0.003$), and intergroup differences were significant for the number of lymph nodes dissected from both the upper mediastinum (RAMIE: 10.7 ± 9.7 vs. MIE: 6.3 ± 9.3 , $P = 0.032$) and abdomen (RAMIE: 12.2 ± 8.7 vs. MIE: 7.8 ± 7.1 , $P = 0.007$). The five-year overall survival did not differ between the two groups (RAMIE: 69% vs. MIE: 59%, $P = 0.737$). Deng *et al.*^[45] showed that RAMIE may have an advantage for lymphadenectomy (mean: 20.6 ± 8.8 vs. 17.9 ± 7.7 ; $P = 0.048$) over MIE without increasing the risk of major postoperative complications. A recent propensity-matched analysis of patients undergoing modified Ivor Lewis esophagectomy also showed that the median total lymph node yield was 27 (range 13-84) in the RAMIE group compared to 23 in the MIE group (range 11-48). With a P -value of 0.053, their results suggest a trend towards improved lymphadenectomy with RAMIE^[46]. These studies

Table 3. Intrathoracic anastomosis in RAMIE

Intrathoracic anastomosis methods	Merits	Limitations
Hand-sewn	Can take full advantage of robot-assisted hand-sewing. Can be performed when the length is insufficient for staple anastomosis	Operative field is not satisfactory in the posterior wall anastomosis
Overlap (linear stapler × 1) + Hand-sewn	No need for additional mini-thoracotomy. Lower occurrence of stenosis. Can save stapler. Can take full advantage of robot-assisted hand-sewing	Cannot completely remove tissue poorly supplied with blood. Need a longer tubular stomach and esophageal end than circular stapler
Function (linear stapler × 2)	No need for additional mini-thoracotomy	Need a longer tubular stomach and esophageal end. Cannot completely remove tissue poorly supplied with blood
Triangular stapling (linear stapler × 3)	A reportedly lower rate of anastomotic complications. Lower occurrence of stenosis	The need to intrathoracically staple three times in three directions is a technical challenge
Circular stapler	Relatively easy to perform. Can completely remove tissue poorly supplied with blood	Need an additional mini-thoracotomy. Need an extra circular stapler. Higher occurrence of stenosis

RAMIE: robot-assisted minimally invasive esophagectomy

demonstrate that RAMIE may be more effective for extensive LND than MIE or OE. Recurrent nerve palsy is a complication that is especially associated with lymph node dissection in the superior mediastinum. In the ROBOT trial, the recurrent nerve palsy rate was 9%^[31]. However, Park *et al.*^[47] showed a significant learning curve on RLN palsy rates, which dropped from 55% to 0% after performing 20 cases in their study. The length of the learning curve for RAMIE has been reported to be 20-70 cases^[8,18].

ROBOTIC INTRATHORACIC ANASTOMOSIS

The robotic intrathoracic anastomosis can be hand-sewn or performed with linear or circular staplers. Although complete hand-sewing takes full advantage of robot assistance, it appears posterior wall anastomoses are technically challenging because of the deep and narrow operative field^[48]. Wang *et al.*^[49] showed side-to-side anastomosis to be a promising approach with the advantages of there being no need for additional mini-thoracotomy and a lower incidence of stenosis. In their report, the authors also emphasized the usefulness of the barbed knotless suture. Another recent study reported similar satisfactory outcomes with end-to-side anastomosis^[50]. Those authors concluded that end-to-side anastomosis requires a shorter length of the esophageal end, and section with poor blood supply was removed by a second stapler, which may ensure a good blood supply to the anastomosis. Triangular stapling is another anastomotic technique, which is reportedly associated with a lower rate of anastomotic complications^[51]. However, stapling three times in three directions would seem to present a great technical challenge intrathoracically. Recently, Han *et al.*^[52] reviewed diverse ways of intrathoracic anastomosis. Among these anastomotic methods, mortality was equivalent, but the anastomotic leak rates differed. Further large clinical trials are still needed. In general, each method has its merits and demerits. Surgeons should determine the anastomotic method of every single case with the final aim of maximizing patient benefits. The methods used for anastomosis in RAMIE are summarized in Table 3.

TRANSTHORACIC VS. TRANSHIATAL RAMIE

As with MIE, different variations of RAMIE have been established. Transthoracic RAMIE is one of the most commonly used approaches. It has a wide operative field, and after posterior and middle mediastinal LND, superior mediastinal LND can be performed in this operative field. However, destruction of the thoracic wall and pleura are unavoidable and differential lung ventilation is still needed. In 2003, Talamini *et al.*^[10] reported the first series of transhiatal RAMIE. Conventional transhiatal MIE has been proven as a less

Table 4. Transthoracic vs. transhiatal route in RAMIE

RAMIE	Merits	Limitations
Transthoracic	Wide operative field. Superior mediastinum lymph node dissection can be performed in the same operative field	Thoracic wall and pleura destruction are unavoidable. Differential lung ventilation is still needed in most case
Transhiatal	No need for thoracic wall destruction. No pleurotomy. No need of differential lung ventilation. No need for a change in body position. Almost no postoperative respiratory complications	Narrow operative field. Need a decent experience for mediastinum lymph node dissection under mediastinoscopy

RAMIE: robot-assisted minimally invasive esophagectomy

invasive operative method but oncologically inferior to radical esophagectomy^[53]. Although lymph node dissection of the lower mediastinal field is considered to be equivalent to radical esophagectomy, when it comes to the middle mediastinal field, it shows shortages because conventional endoscopic devices suffer from the paralleled right- and left-hand in the deep narrow operative fields. Meanwhile, the robot has articulated instruments and enhanced three-dimensional magnified view, which can move freely in the deep narrow cavity. It has been proven that RAMIE can overcome the limitations of the conventional transhiatal MIE and can dissect lymph nodes equivalent to radical esophagectomy^[54]. Yoshimura *et al.*^[55] showed that transhiatal RAMIE is associated with fewer pulmonary complications (0%) and better postoperative quality of life. However, it requires two LND steps. Posterior and middle mediastinal LND is performed using transhiatal RAMIE, followed by cervical mediastinoscopy for superior mediastinal LND. Mori *et al.*^[56] showed that the radicality of transmediastinal esophagectomy is equivalent to that of transthoracic esophagectomy in terms of the number of harvested lymph nodes and the pathology of surgical margins. Similarly, postoperative pneumonia did not occur in the transhiatal group. Although short-term and long-term outcomes were reported to not be inferior, due to the narrow operative field with the transhiatal procedure and mediastinoscopy, transhiatal RAMIE appears to be a more complex procedure. RAMIE operative routes are summarized in Table 4.

OPERATIVE POSITIONS IN RAMIE

Acute lung injury occurs in 25%-30% of patients after transthoracic esophagectomy, and single lung ventilation has been implicated in its pathogenesis^[57]. Until recently, RAMIE has been performed with the patient in the left lateral decubitus position in a setting of single-lung ventilation. Full lateral decubitus position with a cephalic parallel approach was reported to save some operative time (381 ± 57.7 min)^[58]. However, this approach requires total lung collapse and is therefore, often accompanied by serious pulmonary complications. To overcome the disadvantages of differential ventilation, Palanivelu *et al.*^[59] performed MIE with patients in a prone position. With their large patient cohort, they found that the prone position takes advantage of gravity to displace the lung from the dorsal thoracic structures and the esophagus, and that it has lower respiratory complications and shorter operative times due to the excellent exposure of the operative field and the better ergonomics for the surgeon. Sometimes, the vertebral column may obstruct the view of the operative field. Ruurda *et al.*^[60] reviewed the application of the prone position in RAMIE, with the patient cart of the robot system standing on the patient's side and extending its arms in a direction crossing the longitudinal axis of the patient. In the subsequent abdominal phase, the patient cart must be repositioned in front of the patient's head. This patient cart repositioning is time-consuming^[58]. On the other hand, urgent conversion to a classic thoracotomy, if needed, is probably more difficult with the prone position^[61]. As a solution to overcome this problem, whilst retaining the benefits of the prone position, a relatively complicated position, a modified semi-prone position has been adopted by surgeons around the world^[62]. Operative positions are summarized in Table 5.

Table 5. Operative positions in RAMIE

	Merits	Limitations
Left lateral decubitus position	Similar to open resection and does not require repositioning in the case of a conversion to open surgery	Need single-lung ventilation with more postoperative pulmonary complications.
Prone position	Takes advantage of gravity to displace the lung from the dorsal thoracic structures and the esophagus. Excellent exposure of the operative field. Allows for double-lung ventilation with less postoperative pulmonary complications	Need repositioning in the case of a conversion to open surgery
Semi-prone position	Has benefits of both the prone position and left lateral decubitus position	Relatively complicated

RAMIE: robot-assisted minimally invasive esophagectomy

Table 6. Prospects of RAMIE

1	Tactile function
2	Forceps tip shape change function
3	Automatic forceps switch function
4	Flexible camera
5	Artificial intelligence
6	Miniaturized operating robot body and wrist
7	Break the monopoly of the Da Vinci system

RAMIE: robot-assisted minimally invasive esophagectomy

PROSPECTS FOR RAMIE

Although RAMIE has a number of advantages that can overcome the shortcomings of MIE, there are still many problems that need to be resolved [Table 6]. For example, to perform surgery more safely, if possible we would like to add tactile function to the robot. To shorten the operative time, a forceps tip with shape changing function, automatic forceps switching function, and flexible camera are expected. Artificial intelligence is another exciting feature that is being developed. To reduce interference, we are looking forward to the development and manufacture of an operating robot with a miniaturized body and wrists. In addition, to break the monopoly of the Da Vinci system, many surgical robot companies worldwide are working on the development and manufacture of new robot surgery systems, which could bring lower costs.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Liu J, Motoyama S

Performed data acquisition, as well as provided administrative, technical, and material support: Sato Y, Wakita A, Kawakita Y, Nagaki Y, Fujita H, Imai K, Minamiya Y

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

Open Access



Video-assisted thoracoscopic thymectomy: bilateral approach

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Abstract

Aim: The advantages and feasibility of video-assisted thoracoscopic surgery (VATS) in the surgical management of early resectable thymoma and thymic hyperplasia have largely been described and adopted in many thoracic surgery units. In order to allow for resection of all immunogenic thymic cells in patients with myasthenia gravis, surgical removal of the whole thymus gland including perithymic and pericardiophrenic fatty tissue becomes imperative. It is also important to achieve radical resection and excision in cases of thymoma.

Methods: Numerous technical variations of VATS thymectomy have been reported in literature. In this study, the surgical technique of a minimally invasive, extended thymectomy through a bilateral approach is illustrated with key features highlighted.

Results: In our experience, no conversion to the open transternal approach, surgical mortality or major complications were observed; the median length of hospital stay was 3 days.

Conclusion: Bilateral video-assisted extended thymectomy is an effective, safe and well-tolerated approach, with surgical benefits and clinical outcomes similar to other thoracoscopic techniques.

Keywords: Thymoma, video-assisted thoracic technique, thymectomy, bilateral video-assisted thoracoscopic surgery



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INTRODUCTION

Since the origin of this procedure, conventional open thymectomy has been considered the gold standard for the treatment of patients with thymomatous masses^[1]. A gradual transition to minimally invasive techniques though, has become evident within the surgical community. In 1993, Coosemans *et al.*^[2] reported the first cases of video-assisted thoracoscopic surgery (VATS) thymectomy as a safe and effective approach, with or without additional trans-cervical incision.

With the improvement of technology, however, in terms of optical and surgical instrumentation, VATS thymectomy has become increasingly popular. Compared to the standard open technique, minimally-invasive thymectomy has the advantages of reducing surgical trauma, less intraoperative blood loss and duration of postoperative pleural drainage, less postoperative pain, reduced hospital length of stay, better aesthetic result, rapid recovery of lung function and lower complications^[3].

Many retrospective studies comparing open trans-sternal thymectomy to VATS thymectomy have reported no significant difference in terms of adverse events, surgical extent, rate of R0 resection, peri- and post-operative complications. Otherwise, faster recovery times were demonstrated in patients treated with bilateral thoracoscopic thymectomy for patients with MG^[4].

Worldwide, VATS is now used in the surgical treatment of early resectable thymomas and thymic hyperplasia in many thoracic surgery units. In the literature, numerous technical variations to VATS thymectomy have been described and the final choice depends on the individual surgeon's preferences and expertise. A bilateral approach may achieve a more radical thymectomy, as described by some surgeons, either alone or together with an additional cervical or sub-xyphoid incision^[4-8].

The choice of the first side of the thorax to be approached varies according to the surgeon's experience and preference. The intraoperative steps may also vary: some surgeons prefer to start dissection from the right side and divide the thymic veins from the left, while others approach the thymic veins from the left first, and some authors start dissecting the thymic veins from the right^[6,9,10].

In this study, the surgical technique of a minimally invasive, extended thymectomy through a bilateral approach is illustrated with key features highlighted.

METHODS

All operations were carried out under general anaesthesia with double-lumen intubation. The patients were placed in a semi-supine decubitus position with the hemithorax raised to about 30° from the horizontal plane, and widely prepped to allow simple exposure of both sides. The entire chest is elevated from the table by a soft gel roll placed under the spine with both arms extended overhead for wide exposure of the two hemithoraces [Figure 1]. The head is also flexed, in order to move the thymus inferiorly into the mediastinum, out of the cervical neck. The assistant stands beside the operating surgeon, while the scrub is placed facing the operating surgeon.

Step 1: right side

The right side is accessed first. With the surgical table tilted slightly towards the left, an initial 10-mm trocar is inserted through the 5th intercostal space (ICS) along the anterior-axillary line; two additional 5-mm ports are then placed in the fifth ICS along the mid-clavicular line, and in the third ICS along the mid-axillary line respectively [Figure 1]. CO₂ insufflation is used during the whole procedure (the pressure is commonly maintained at 6 mmHg, and flow around 6 mL/min), in order to favour right lung collapse and facilitate dissection. A 30-degree (5 mm or 10 mm) scope is used to allow visualisation of the mediastinal structures from multiple perspectives.

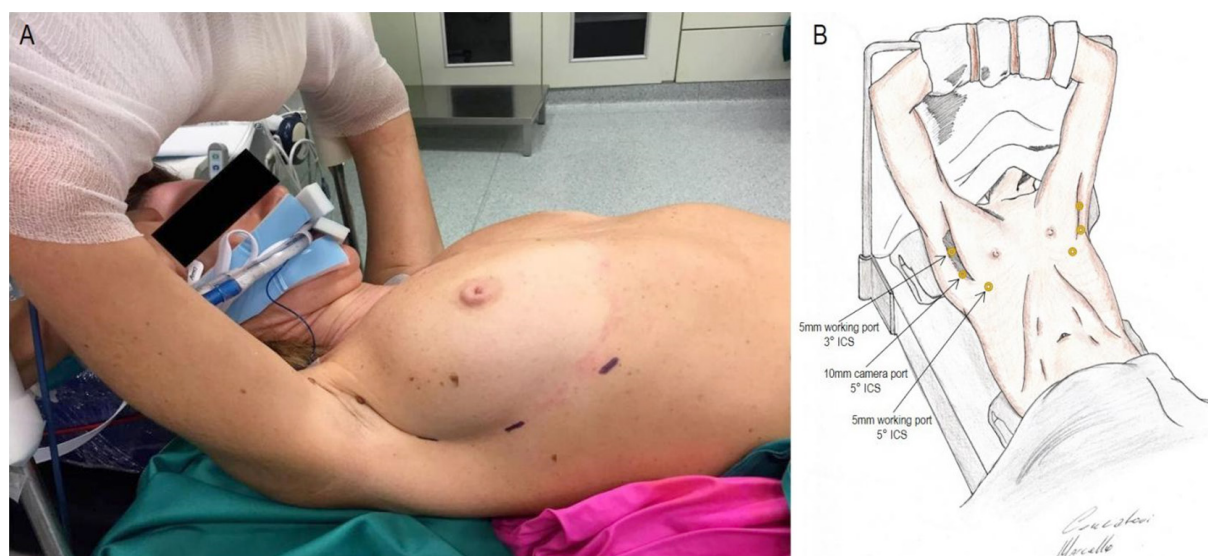


Figure 1. Young patient positioned for bilateral video-assisted thoracoscopic surgery (VATS) thymectomy; right-sided approach. The entire chest is lifted from the table by a soft gel shoulder roll with both arms extended overhead to allow full exposure of the bilateral hemithoraces (A); port placement for bilateral VATS thymectomy (B). ICS: intercostal space

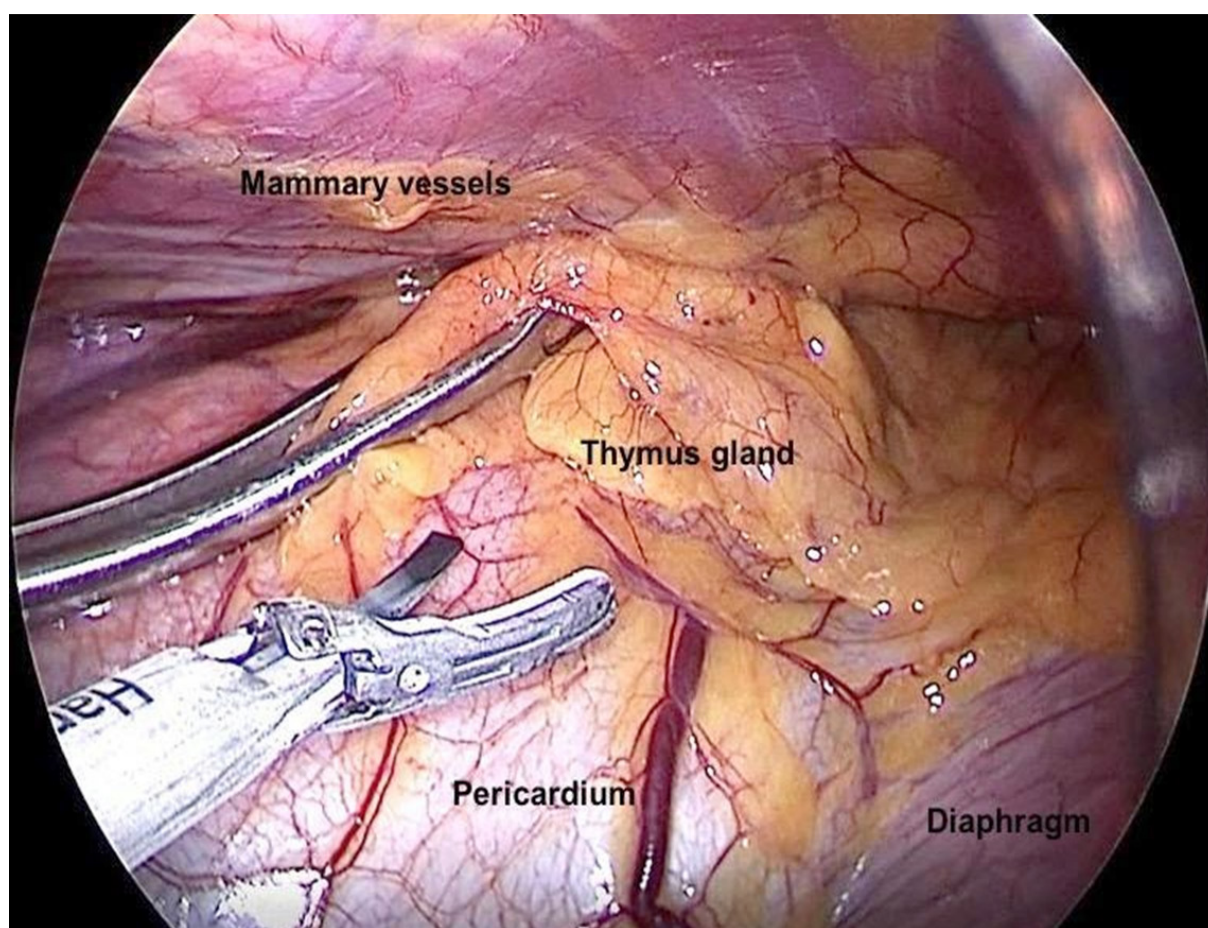


Figure 2. Right-sided view: the dissection starts inferiorly by mobilizing the thymus from the pericardium

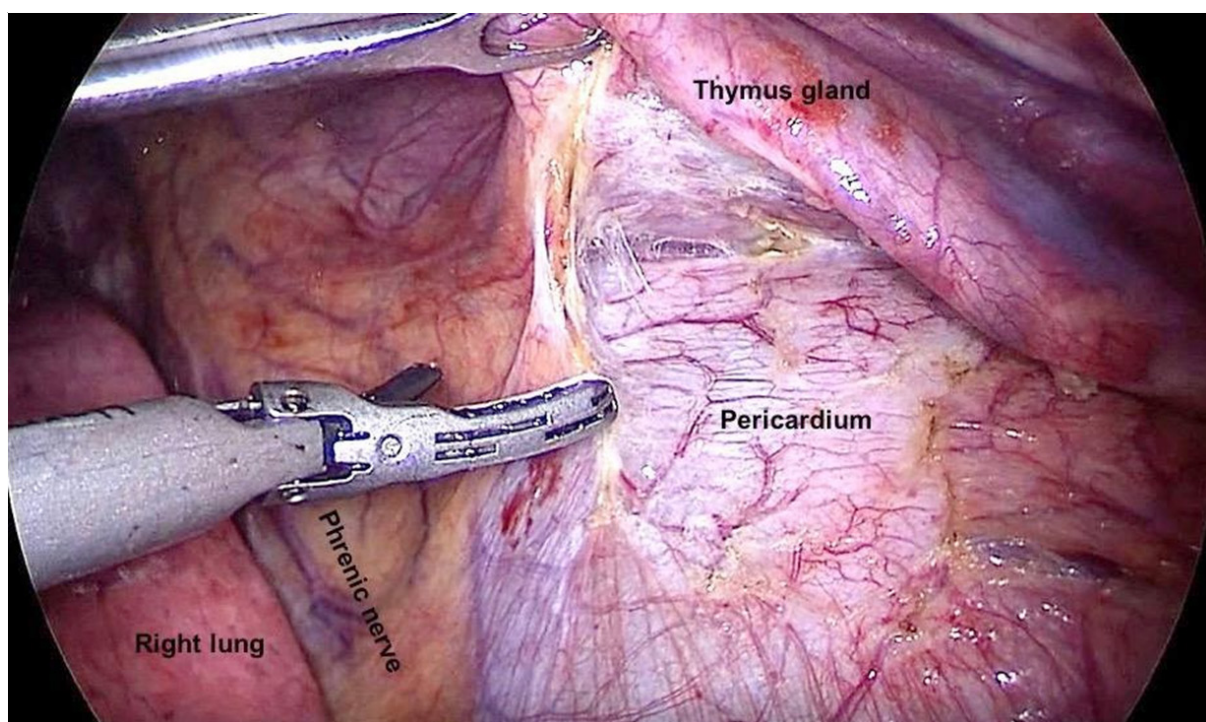


Figure 3. Right-sided view: the thymic dissection is performed cranially along the phrenic nerve with a harmonic scalpel. The main anatomic landmarks are indicated

After inspection of the mediastinal and pleural surfaces to confirm the absence of metastases, the dissection begins by grasping the fat pad in the right cardiophrenic angle [Figure 2]; the mediastinal pleura is now opened anterior to the right phrenic nerve with a harmonic scalpel (Ultracision Harmonic; Johnson & Johnson, NJ) [Figure 3]. The right lobe of the thymus gland and surrounding fat are mobilized from the diaphragm inferiorly, the pericardial surface medially, and from the posterior aspect of the sternum [Figure 4]. The dissection is carried superiorly, in a caudo-cranial direction, along the right phrenic nerve in order to identify the right internal mammary vein and to reach the confluence of the superior vena cava and the left innominate vein [Figure 5]. Care must be taken to prevent stretch and thermal injury to the nerve and mediastinal vessels.

Dissection is achieved by combining blunt and sharp dissection. The left innominate vein is clearly identified and the right cervical horn can be grasped and gradually pulled down into the pleural cavity, freeing it up from the surrounding fat tissue, in order to achieve complete mobilization with identification of the thymo-thyroid ligaments, which are then divided. The left horn is visualised and dissected with the same technique from the right hemithorax.

The body of the thymus gland is mobilized downwards in order to expose the thymic veins (veins of Keynes), which are dissected and divided along the innominate vein, using an endoscopic clip applicator (click a V, GrenaR or titanium clips) or with an energy device. All arterial communications with the internal mammary arteries are divided; after mobilisation of both the superior poles, dissection can now be continued towards the left chest.

After completion of the right-sided dissection, the retrosternal space with the left parietal pleura is widely opened, and the specimen is then pushed into the left pleural cavity.

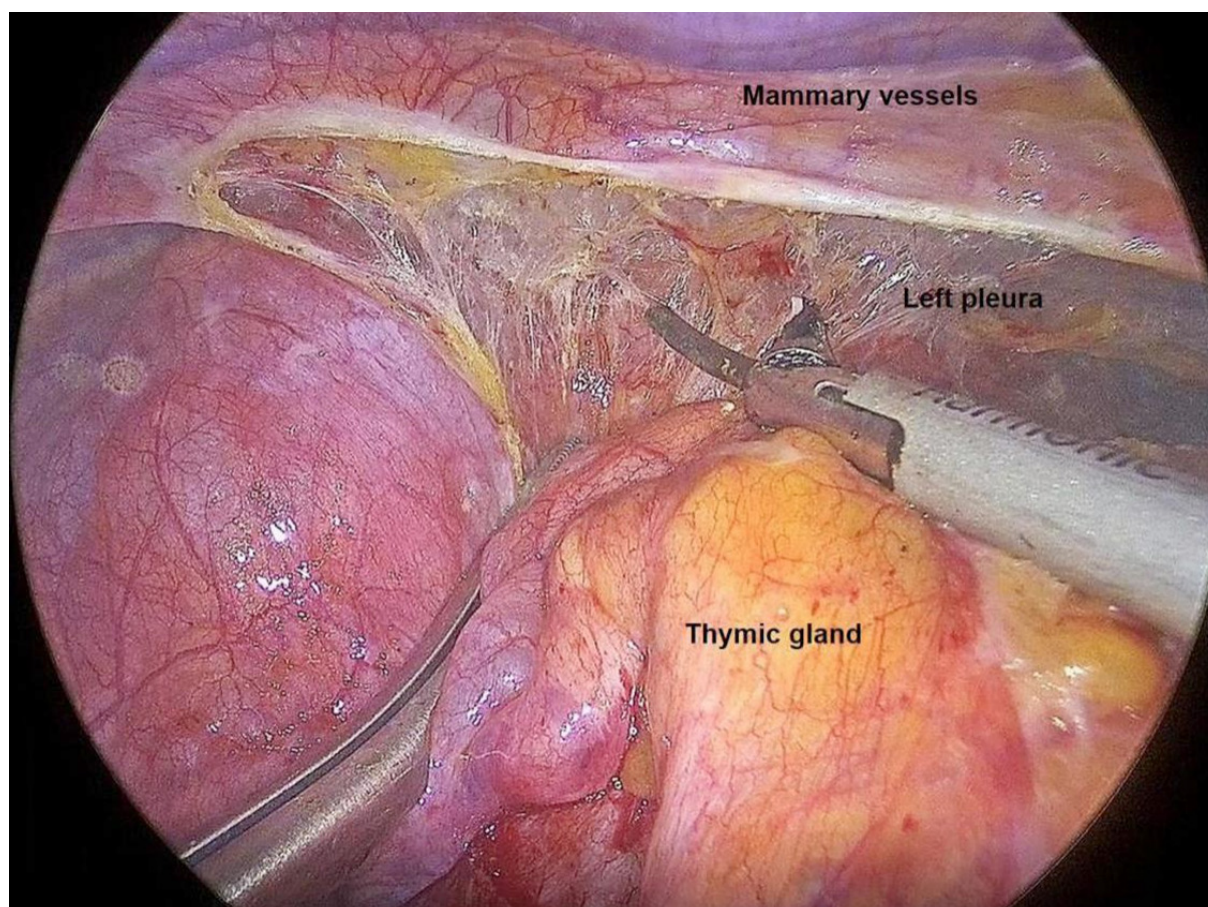


Figure 4. Right-sided video-assisted thoracoscopic surgery view: the right lobe of the thymus and surrounding fat are mobilized from the posterior aspect of the sternum. The anatomic landmarks are indicated

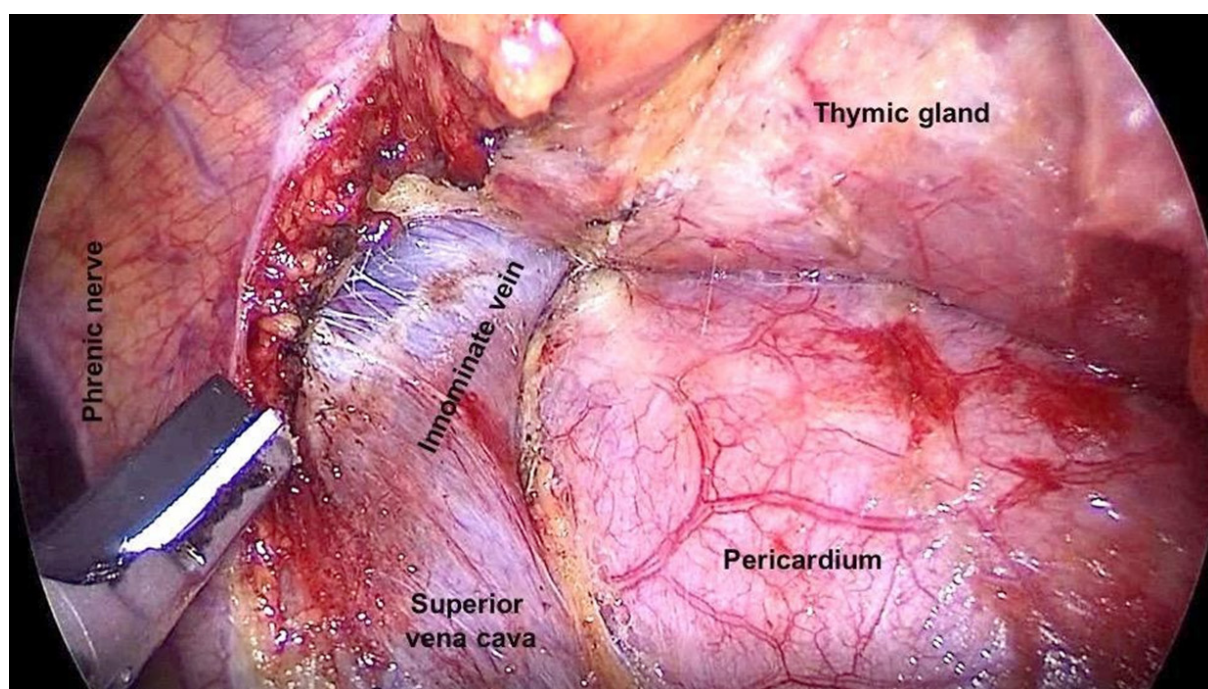


Figure 5. Right-sided video-assisted thoracoscopic surgery view: dissection at the level where the left innominate vein joins the superior vena cava. The anatomic landmarks are indicated

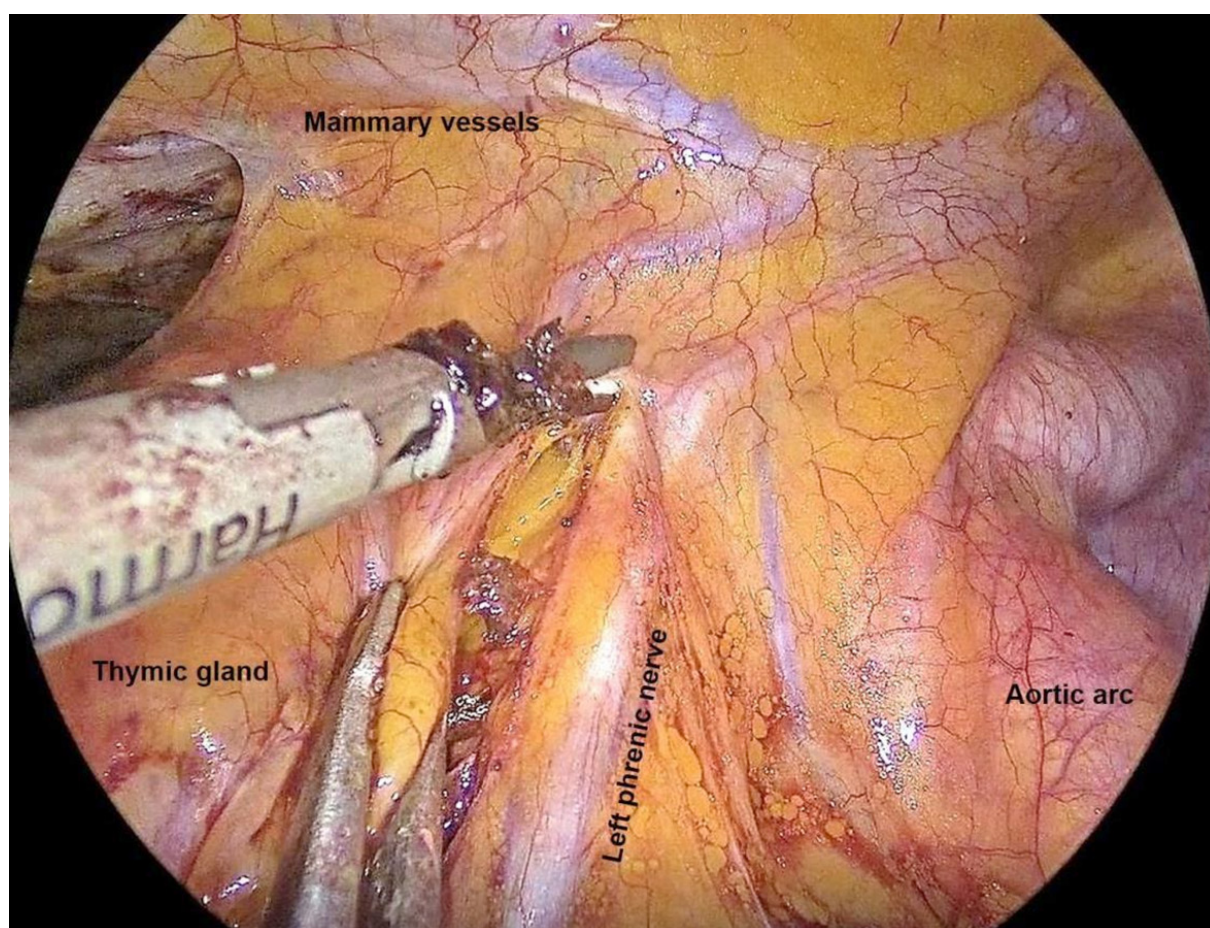


Figure 6. Left-sided video-assisted thoracoscopic surgery view. The thymic gland is freed from the left phrenic nerve with a harmonic scalpel (Ultracision Harmonic; Johnson & Johnson, New Brunswick, NJ) and the dissection continues cephalad in order to access the thoracic inlet and the previously dissected right side of the procedure

Step 2: left side

Right lung ventilation is re-initiated. The high-definition camera is inserted through a 5- or 10-mm port, placed in the 5th ICS along the mid-axillary line within the inframammary fold. Two additional ports are then inserted under direct visualisation; a 5-mm port is inserted through the 3rd ICS along the anterior axillary line and another 5-mm port is placed in the 5th ICS along the mid-clavicular line.

Next, the dissection starts at the level of the left cardiophrenic angle, by grasping the thymus and the fat pad anterior to the left phrenic nerve. The thymus gland is mobilized by dissecting from the pericardial layer. When the retrosternal plane is opened widely, the dissection continues cranially along the left phrenic nerve, in order to join the thoracic inlet superiorly, and the previous site of dissection on the posterior aspect of the sternum [Figure 6].

All thymic tissue and the anterior mediastinal fat are now completely mobilized. Removal of the specimen is finally performed using an Endobag after enlarging the 10-mm port site. Usually, at the end of the procedure, a 24-F chest tube is placed in both hemithoraces through the lowest existing port incision for postoperative drainage of fluid and air. Correct lung re-inflation is then directly visualized and all port sites are closed with absorbable sutures (Figure 7 - final right-side view).

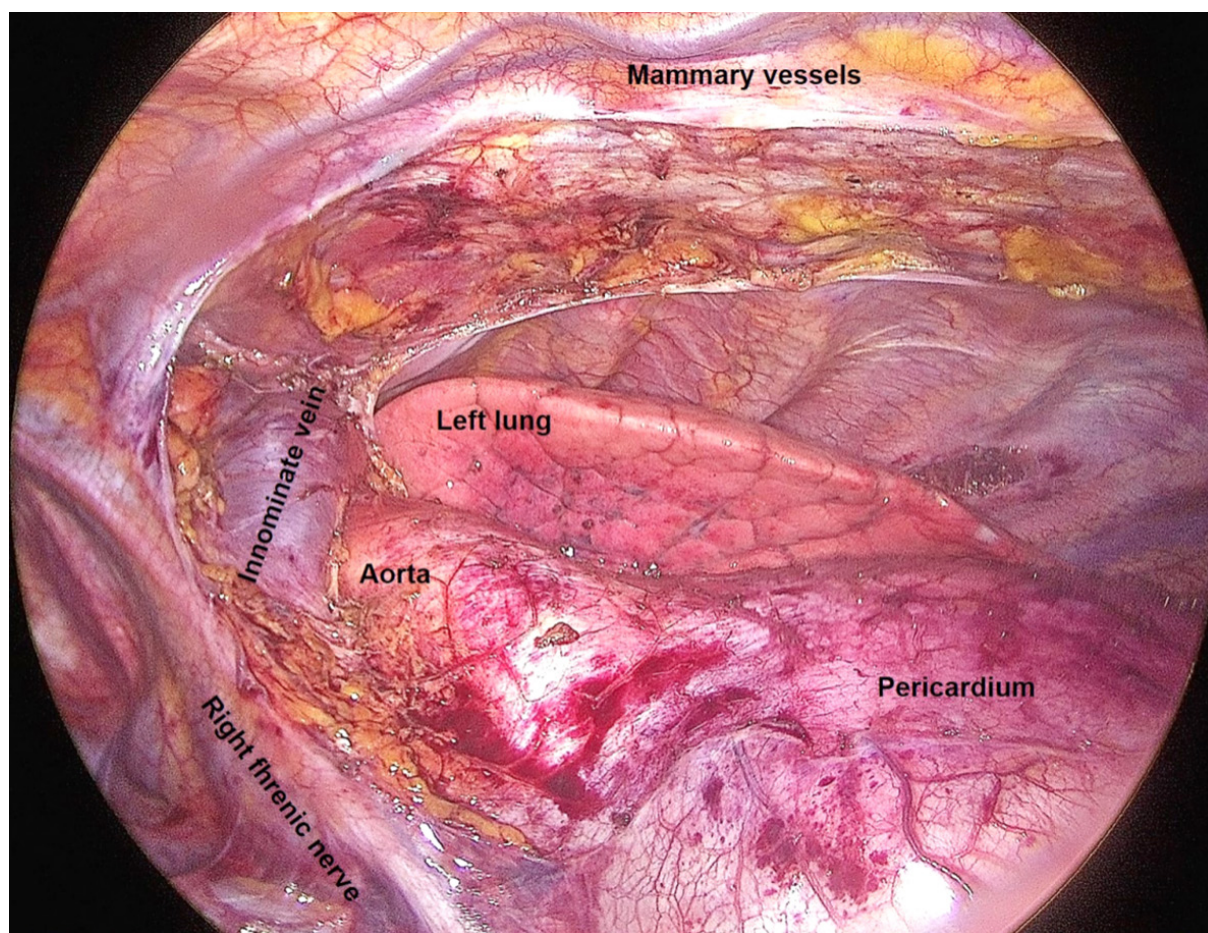


Figure 7. Final view from the right; the anatomic landmarks are indicated

Tips and tricks

- (1) We suggest performing VATS thymectomy using double-lumen intubation, which may be useful in case of lung infiltration from a thymoma.
- (2) In order to avoid the risk of capsular break and spillage of thymic tissue, we recommend avoiding grasping of the thymus gland directly, i.e., a “touch-free” technique is preferable.
- (3) It is helpful to perform all phases of the surgery and the entire dissection of the mediastinal fat with energy-based tissue sealing devices such as the harmonic scalpel (Ultracision Harmonic; Johnson & Johnson, NJ) or electrothermal bipolar tissue sealing system (LigaSure, Valleylab Inc., USA), both of which can also be used for dividing small thymic vessels.
- (4) During minimally invasive thymectomy, CO₂ insufflation in the chest cavity offers various advantages: faster lung deflation; increased operative space by pushing the mediastinum and diaphragm towards the opposite chest cavity and away from the operative area; continuous circulation of cautery smoke and aerosolized ultrasonic vapor during dissection to allow better visibility of the surgical field; and it helps in dissecting and visualizing tissue planes.
- (5) Bilateral VATS thymectomy offers the possibility to perform the whole thymic resection from either the right or left side, in the event of pleural adhesion on one side as both phrenic nerves are clearly visualized.

In our experience, no conversion to the open transternal approach, surgical mortality or major complications were observed. The median operative time and blood loss were 150 min (+/- 20 min) and 20 mL (+/- 20 mL) respectively and the median length of hospital stay was 3 days.

DISCUSSION

The aim of thymectomy in patients with myasthenia gravis (MG) is the complete removal of the thymus and perithymic tissue to eradicate all immunogenic thymic cells and potentially viable thymic tissue in patients with MG to minimize disease persistence or increasing relapse rates. In cases of malignancy when a thymoma is diagnosed, it is still crucial to achieve radical *en bloc* excision of the residual thymic gland to improve both overall survival and the risk of local recurrence.

With a left-sided approach for thymectomy, dissection of fat tissue in the right cardio-phrenic angle and within the confluence of the superior vena cava and innominate vein can be difficult, while the resection of the thymus gland with fat tissue in the left cardio-phrenic angle and at the level of the aorto-pulmonary window may be limited with a right-sided approach. On the contrary, the bilateral view improves the approach to the left innominate vein and offers a clear and close view of both phrenic nerves. Moreover, the bilateral view might be especially helpful in thymomas.

An additional cervical incision within the neck may be helpful for a more extended excision of all residual thymus at the level of the upper cervical poles but in our experience, the bilateral VATS technique can safely achieve radical dissection of both superior thymic horns. Some sort of bilateral view, especially of the contralateral phrenic nerve, might be achieved by adding a sub-xyphoid port to the unilateral approach (see below).

We believe that correct positioning of the trocars and the patient's position are crucial to facilitate surgical dissection, avoid instrumental conflicts within the thorax and to reduce operating time. We routinely use an energy-based tissue sealing device during the whole procedure (ultrasound or radiofrequency are equivalent depending on personal experience and preference) for tissue handling, dissection and sealing vessels (Keynes veins).

Among the various minimally invasive approaches, the subxiphoid thymectomy described by Kido *et al.*^[11] in 1999 is gaining interest and popularity among thoracic surgeons. The two main advantages of this approach are reduction of postoperative pain and cosmetic results because of the small incisions (1 or 2 ports for access) and the possibility to avoid intercostal nerve damage. As shown by Suda *et al.*^[12], in comparison with a lateral VATS approach, the subxiphoid thymectomy is associated with reduced consumption of postoperative analgesics and perioperative blood loss. A similar operative time was observed in the two groups^[12]. This technique seems to be able to overcome some technical difficulties of the VATS operation, such as the small working space, different viewpoint from a median sternotomy and bilateral phrenic nerve control. On the other hand, the subxiphoid approach is not widely used because of its unfamiliarity among thoracic surgeons and difficult intraoperative control of bleeding in the event of major vessel injury such as bleeding of the left innominate vein.

The definition and indications for VATS thymectomy in the treatment of early-stage thymomas are summarized in the ITMIG recommendations^[13]. Some authors disagree with a minimally invasive approach for large tumours because the dissection might be difficult and tumor manipulation might translate into intraoperative seeding of the pleural space, which would compromise the procedure^[14].

Nevertheless, some earlier studies comparing robotic-assisted thymectomy with trans-sternal thymectomy showed that large thymic tumors can be managed by the robotic approach, which has improved three-dimensional visualization, increased freedom of instrument motion for precise dissection and permits radical dissections, even of thymomas > 4 cm in diameter, while reducing the risk of capsular injury and providing all the benefits in postoperative recovery of the minimally-invasive approach to the patient^[15].

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patients for publication of the manuscript and associated images.

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Review

Open Access



Robotic esophagectomy: the evolution of open esophagectomy to current techniques and a review of the literature

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Abstract

Esophageal cancer persists as one of the most common causes of cancer-related death and 5-year survival remains poor at 20%. Surgical resection is the gold standard for treatment and cure, and the development of minimally invasive surgery has increased the popularity of robotic-assisted minimally-invasive esophagectomy. The benefits described include less morbidity and greater patient satisfaction compared to open techniques. Nevertheless, institution capabilities and surgeon experience are strong determinants of whether a robotic program will be adopted for oncologic esophageal care. Thus, we review the available literature regarding the history of esophagectomy, evolution to minimally invasive approaches, the introduction of robotic-assisted esophagectomy including its respective outcomes in comparison to open and minimally invasive approaches, and future directions.

Keywords: Minimally invasive, esophageal cancer, esophagectomy, lymph node dissection, robotic-assisted esophagectomy, Ivor Lewis, McKeown, transhiatal

INTRODUCTION

Globally, esophageal cancer is the eighth most common cancer in the world and the sixth most common cause of cancer death^[1]. Despite many advances in treatment, 5-year survival remains poor at 15%-25%;



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among all patients^[2], and the American Cancer Society estimates approximately 17,650 new esophageal cancer cases will be diagnosed in 2020, with an estimated 16,170 cases resulting in death^[3]. While esophageal resection, with or without neoadjuvant chemoradiation therapy, remains the most likely route of cure for these patients, less than 50% present with locoregional disease^[4], a prerequisite for surgical intervention^[5]. Furthermore, despite the oncologic benefits, traditional open esophagectomy is associated with considerable morbidity and mortality, complication rates range from 26% to 41%, with perioperative mortality as high as 4%-10%^[4-6].

Fortunately, of those patients who are candidates, survival increases to 40% among patients who successfully undergo curative surgery^[2], and resection can also palliate the debilitating symptoms of dysphagia that often accompany the disease^[7]. Hence, surgical resection remains the gold standard for cure and definitive symptom management. The choice of technique depends on several factors with the location of the tumor, an institution's resources, and surgeon experience being the most relevant^[7]. Traditionally, open esophagectomy (OE), utilizing either a transthoracic (OTTE) or transhiatal (OTHE) approach has been the surgical treatment of choice with Ivor Lewis, via thoracotomy and laparotomy; McKeown via thoracotomy, laparotomy, and cervical incision; and Transhiatal via laparotomy and cervical incision comprising the standard methods of resection.

Minimally invasive techniques were introduced in the early 1990s to help lessen the morbidity associated with this procedure and have increasingly become more common over the last 30 years^[5,8]. They were designed to decrease the high morbidity and mortality associated with open resection through utilization of a combination of laparoscopy and thoracoscopy^[9]. Although multiple studies have demonstrated a decrease in perioperative complications, the data describing oncologic outcomes, specifically regarding the extent of lymph node dissection, are varied.

More recently, robotic-assisted minimally invasive esophagectomy (RAMIE) is an alternative to standard minimally invasive esophagectomy (MIE), and has been increasingly applied to the treatment of esophageal cancer^[10]. Its benefits include a superior quality 3D image and free articulation of the tips of the robotic instruments^[10] that can assist in more precise movements^[10], especially enhancing the lymph node dissections. More and more studies are demonstrating that robotic approaches to esophagectomy reduce morbidity and mortality, and patients report better overall quality of life, physical function, and less fatigue and pain at three months after surgery^[11]. Nonetheless, while robotic-assisted esophagectomy is a promising procedure, technical difficulties, long operating times, and lack of experience make this procedure difficult to adopt for many hospitals^[12]. Today, convincing data on how beneficial and to what extent RAMIE resection provides superior perioperative and oncologic outcomes, increased cost-effectiveness, and improved quality of life remain unclear^[5]. The aim of this work is to review the available literature regarding robotic-assisted esophagectomy and its origins; compare perioperative, oncologic, and quality of life outcomes with open and minimally invasive approaches; and explore future directions.

MATERIALS AND METHODS

A literature search was conducted in Medline (PubMed), which queried the keywords "Esophageal Cancer, Esophagectomy, Open Esophagectomy, MIE, RAMIE, Robotic Esophagectomy, Lymph Node Dissection, Ivor Lewis, McKeown, and Transhiatal Esophagectomy". All articles that were in the English language and discussed open, laparoscopic, thoracoscopic, combined approaches, and robotic-assisted techniques were reviewed. For data acquisition, articles were included if they met the above inclusion criteria and were comparative studies of minimally invasive and open esophageal resection, minimally invasive and robotic resection, open and robotic resection, or all three techniques with the goal to detail their historical development, contemporary outcomes and future directions.



Figure 1. Tork Esophagectomy. Franz Tork first described resection of the thoracic esophagus using a rubber tube. Used with permission: *The Annals of Thoracic Surgery* 1965;4(85):1497-1499.

RESULTS

History of esophagectomy and open techniques

To better understand advancements in esophageal surgery, it is important to take a moment to review the history of esophageal resection and the complexities of this procedure. Ivor Lewis said it best when he stated, “there is little doubt that the successful outcome of curative surgery for esophageal carcinoma remains one of the great challenges of surgical practice”. Historically, innovation drove many advancements in treatment of esophageal disease dating back to 1913. Franz Tork first described resection of the thoracic esophagus using a rubber tube to create an extra-anatomic reconstruction [Figure 1]^[8,13].

Amazingly, the patient survived for 13 years, leading to the evolution of surgical procedures to resect the esophagus and replace it with a gastric conduit^[14]. Subsequent versions have included the Ivor Lewis (IL) esophagectomy via right or left thoracotomy with subsequent two-field esophagectomy^[15]; the McKeown esophagectomy involving a three-field esophagectomy with thoracotomy and laparotomy and terminating with a cervical anastomosis^[16]; and Orringer and Sloan’s transhiatal esophagectomy (THE), involving laparotomy and cervical anastomosis^[17].

The Achilles heel of esophageal cancer surgery has always been the high complication rates, even when performed at high-volume centers. Despite improvements over the years, the rates of morbidity and mortality of open esophagectomy remain high and are estimated to range 30%-60% and 5%-10%, respectively, depending on patient comorbidities and place of operation^[8]. Mortality has been shown to decrease to < 5% in centers that perform more than 100 esophagectomies per year^[8]. Although technical advances have improved the rate of anastomotic leak, consequences of a leak into the chest were and continue to be devastating and difficult to manage^[18]. Notably, transhiatal esophagectomy has historically demonstrated reduced mortality rates from anastomotic leak resulting in less severe consequences compared to the IL approach, although it does have a higher overall leak rate. Meta-analysis has further demonstrated a mortality rate of 6.3% for transhiatal esophagectomy compared with 9.5% for the IL

Table 1. Laparoscopic, thoracoscopic and robotic approaches to esophagectomy by

1.	Hybrid laparoscopic with thoracoscopy-assisted/mini-thoracotomy 2-field IL esophagectomy
2.	Hybrid transthoracic with laparotomy or hand-assisted laparoscopic 2-field IL esophagectomy
3.	Total laparoscopic and thoracoscopic 2-field IL esophagectomy
4.	Hybrid laparoscopic with thoracotomy three-field McKeown esophagectomy
5.	Hybrid thoracoscopic with laparotomy/hand-assisted laparoscopic three-field McKeown esophagectomy
6.	Total laparoscopic and thoracoscopic three-field McKeown esophagectomy
7.	Total laparoscopic THE
8.	Total laparoscopic inversion esophagectomy
9.	Total laparoscopic Vagus-sparing esophagectomy
10.	Combination of abdominal and thoracic phases using VATS/mini-thoracotomy/thoracotomy and laparoscopy/mini-laparotomy/hand port or full laparotomy (so-called hybrid robotic esophagectomy)
11.	Total robotic IL esophagectomy
12.	Total robotic THE
13.	Total robotic three-field McKeown esophagectomy

IL: Ivor Lewis; THE: transhiatal esophagectomy; VATS: video-assisted thoracoscopic surgery

approach^[18,19]. Unfortunately, in practice, this procedure is performed less often, which limits its benefit to the patient.

Minimally invasive techniques

High complication rates, longer recovery times, and the desire for a less invasive procedure is what led to the innovation driving minimally invasive surgery. Specifically for esophagectomy, the definition of a MIE includes varying thoracoscopic and laparoscopic approaches for esophageal resection based on the location of the tumor, clinical stage, and patient characteristics^[20,21]. In 1991, Dallemagne *et al.*^[22] first reported the use of laparoscopy for a hiatal hernia repair, inspiring Cuschieri *et al.*^[23,24] who utilized thoracoscopy for esophagectomy in 1992. In 1993, Collard *et al.*^[25] sophisticated the technique, and, in 1995, DePaula *et al.*^[26] was the first to perform a completely laparoscopic THE. Today, many different versions of MIE are performed^[27] employing several combinations of approach using laparoscopic and thoracoscopic techniques [Table 1, Items 1-9].

Indications for minimally-invasive esophageal resection approaches are similar to those for open esophagectomy and include esophageal cancer, failure of endoscopic ablation and/or resection for high grade dysplasia secondary to Barrett's esophagitis, stricturing of the esophagus, and the sequelae of achalasia and Chagas disease known as "burned out esophagus"^[27]. Relative contraindications to its use are known extensive pleural or abdominal adhesions, with absolute contraindications involving the inability to use single-lung ventilation because of previous resection or poor lung function. As expected, surgeon comfort and experience have proven to be additional important factors.

Reviewing the operative steps of MIE, they are similar to robotic esophagectomy with the exception of port placement and can help to better define the benefits of robotic approaches. In general, the benefits have proven to be great. For minimally invasive IL esophagectomy, Levy *et al.*^[28,29] and Luketich *et al.*^[30] best described the operative steps including commencing with an abdominal phase to mobilize the stomach/proximal duodenum and create the conduit. This is then followed by a thoracic phase where the specimen is resected and anastomosis completed. Advantages include good oncologic "en bloc" lymph node dissections of the stomach and thoracic esophagus, decreased incidence of anastomotic leak, and decreased injury of the recurrent laryngeal nerve^[27]. Disadvantages include contamination of the chest, which can lead to longer hospital stays, decreased quality of life if anastomotic leak occurs, and increased pulmonary morbidity secondary to the need for single-lung ventilation^[27].

Suzuki *et al.*^[31] best described the McKeown three-field esophagectomy using a minimally invasive approach entailing a thoracic phase similar to a minimally invasive IL approach, an abdominal phase

Table 2. Review of short-term outcomes of minimally invasive esophagectomy vs. open esophagectomy

Study	Design	Period	OE:MIE	Respiratory complications	Surgical complications	30 day mortality
Biere <i>et al.</i> ^[33] Europe (2012)	RCT	2005-2008	56:59	OE > MIE	=	=
Seesing <i>et al.</i> ^[34] Netherlands (2017)	ND	2011-2015	433:433	=	OE < MIE	=
Mamidana <i>et al.</i> ^[35] England (2012)	ND	2005-2010	6347:1155	=	OE < MIE	=
Nozaki <i>et al.</i> ^[36] Japan (2018)	P	2006-2013	109:101	OE > MIE	OE < MIE	=
Takeuchi <i>et al.</i> ^[37] Japan (2018)	ND	2011-2012	3515:3515	=	OE < MIE	=

MIE: minimally invasive esophagectomy; OE: open esophagectomy; RCT: randomized control trial; ND: national data; P: prospective data; =: equivalent

which also includes a dissection similar to minimally invasive IL, followed by termination after a cervical anastomosis is completed^[27,31]. Advantages include excellent oncologic “en bloc” lymph node dissections of the stomach and thoracic esophagus similar to that of IL in addition to easier management of leaks given the cervical anastomosis^[27]. Disadvantages include increased incidence of recurrent laryngeal nerve injury and oropharyngeal dysfunction compared to IL and increased rates of anastomotic leak^[27].

DePaula *et al.*^[26] best described the minimally invasive transhiatal esophagectomy, which entails starting with the abdominal phase similar to an IL, continuing the esophageal mobilization into the mediastinum, and ending with a cervical dissection, delivering the specimen through the neck and completing the anastomosis. Advantages include decreased pulmonary morbidity secondary to eliminating the thoracotomy/thoracoscopy segment and easy management of cervical leaks^[27]. Disadvantages include increased dysphagia that is oropharyngeal in nature and secondary to recurrent laryngeal nerve injury and access for mediastinal lymph node dissections^[27].

Other techniques described, but not as frequently performed, include vagal-sparing esophagectomy designed to eradicate postoperative complications such as delayed gastric emptying, dumping syndrome, and post-vagotomy diarrhea. Another technique, laparoscopic inversion esophagectomy, does not include lymph node dissection of the mediastinum, and is only suitable for benign disease^[27,28]. For all MIEs, anastomotic techniques have varied. Cervical anastomosis has been described using either a two-layer handsewn, circular or linear stapled anastomotic technique, with thoracic anastomosis employing the same. More recently, the OrVil (Covidien, Mansfield, MA, USA), which is a stapling device utilized trans orally, has touted benefits including the elimination of the technical assistance needed to attach the anvil to the esophagus^[27]. Other technical issues include the decision of whether or not to perform a conduit emptying procedure (pyloroplasty, pyloromyotomy, or Botox injection), gastric ischemic conditioning, or prophylactic thoracic duct ligation, none of which have demonstrated a substantial difference in outcomes^[27].

Robotic esophagectomy

Although the use of minimally invasive techniques has many advantages including lower respiratory complications and equivalent 30-day mortality [Table 2]^[32-37], the use of thoracoscopic and laparoscopic surgery also has many drawbacks. First, visualization using both techniques is limited to two dimensions. Second, with thoracoscopy, the need of the intercostal spaces to function as a fulcrum often leads to nerve injury, postoperative pain, and paresthesias^[27]. As these obstacles have not been unique just to esophagectomy, many have sought to bypass these challenges resulting in the development of robotic surgery using computer-assisted surgical systems. Today, the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA)^[27,38] is the only robotic platform that is currently Food & Drug Administration approved and available in a commercial platform. However, more models are on the horizon.

In 2002, Melvin *et al.*^[38] first reported completion of a robotic esophagectomy, and, in 2003, Horgan described his experience performing the first robotic-assisted THE. Kernstine *et al.*^[39,40] documented the first totally

robotic McKeown three-field esophagectomy 1 year later. It included both the thoracic and abdominal phases followed by cervical anastomosis described for the MIE with differing port placements^[39]. Dunn *et al.*^[41] were the first to describe their longer-term outcomes reporting on their 3-year experience performing THE, and others have more recently described the robotic IL esophagectomy. Today, similar to MIE, there are several additional combinations of thoracic and abdominal phases including VATS/mini-thoracotomy/thoracotomy and laparoscopy/mini-laparotomy/handport or traditional laparotomy (also known as the hybrid robotic esophagectomy, Table 1, Items 10-13).

The use of computer-assisted technology (also known as robotics) provides several advantages including 10-fold magnification and three-dimensional visualization^[27,38,42]. The endowrist provides seven degrees of freedom and works to simulate normal wrist movements, while it employs a motion filter up to 60 Hz that works to reduce tremor^[38,42]. Most importantly, for most uses, the fulcrum of the instrument lies inside the body instead resting on the body wall, which helps to decrease postoperative pain^[42]. Although the depth of the benefits cannot be denied, there are some important disadvantages. Access to robotic platforms can be limited depending on the resources of the host institution. Given the expense attached to their use, specific departments must often be able to establish need to justify the cost, which can prove difficult for smaller centers. Surgeon comfort can be a challenging hurdle to overcome given unfamiliarity with the use of this platform in the aging surgeon population, and lack of training in new graduates. Most importantly, the lack of haptic feedback makes the use of robotic surgery challenging once it is incorporated in one's practice, which can increase the rate of devastating and life-threatening complications in novice users.

Learning curve of minimally invasive and robotic esophagectomy

As stated above, performing minimally invasive or robotic-assisted procedures is technically complex and they have significant learning curves. Decker *et al.*^[43] specifically reviewed the relationship between surgical experience and minimally invasive esophagectomy outcomes and found centers performing 50 or more cases had lower morbidity and mortality rates than centers with less expertise^[27]. They also had more experience performing more complex lymph node dissections. Early estimates of cases needed to obtain proficiency resided around 35-40 operations, with 25 cases used as a benchmark required for competent performance of a lymphadenectomy^[27,43]. Today, the precise number of procedures needed to determine if a surgeon is proficient has still not been definitely established, as Claassen *et al.*^[44] described in their recent review. However, parameters such as estimated blood loss, operative time, the number of lymph nodes retrieved, anastomotic leak rate, duration of hospital stay, and overall complication and mortality rates can serve as benchmarks.

Regarding robotic esophagectomy, the reports have been somewhat varied and recent articles estimate the optimal number to range between 20-80 cases depending on the outcome parameter surveyed^[45-47]. Park *et al.*^[45] retrospectively reviewed 33 patients divided into two groups, the first 20 cases and the subsequent 13. While the operative time, robotic console time, lymph node dissections, and blood loss were similar between the two groups, the incidence of vocal cord palsy was significantly lower in Group 2^[45]. Zhang *et al.*^[46] demonstrated that 26 cases were required to gain proficiency of robotic-assisted McKeown esophagectomy for surgeons experienced in open and thoraco-laparoscopic esophagectomy. More specifically related to the learning curve, they estimated robotic-assisted esophagus dissection would require operations on 26 patients with stomach mobilization requiring 14 operations^[46]. The bedside assistant would need at least nine cases to achieve an optimal technical level of thoracic docking, and 16 cases for abdominal docking^[46]. Park *et al.*^[47] had a more varied range, demonstrating that the number of harvested lymph nodes increased from 25 before 30 cases to 45 after, and vocal cord palsy decreased from 36% before 60 cases to 17% after. Total operative time decreased from 496 to 431 min, rate of anastomotic leakage decreased from 15% to 2%, and the length of stay decreased from 24 to 14 days after 80 cases^[47]. Clearly, the use of robotics adds a level of complexity to the case and requires many hours of training and multiple cases for a surgeon to perfect their technique to decrease the risk to the patient.

Table 3. All reports of robotic esophagectomy published in the literature with technique of surgery and outcomes

Author	Cases (n)	Operation	Robot time, min	Total time, min	EBL, mL	ICU stay, day	Hospital Stay, day	Leak rate, %	30-d mortality, %	Lymph nodes, mean	Survival
Melvin <i>et al.</i> ^[38]	1	HRILE	108	462	NR	NR	12	NR	NR	NR	NR
Guilianotti <i>et al.</i> ^[48]	5	HRMKE	NR	490	NR	NR	NR	40	NR	NR	1 death
Horgan <i>et al.</i> ^[49]	1	RTHE	52	246	50	2	NR	0	NR	NR	NR
Kernstine <i>et al.</i> ^[40]	1	RMKE	260	660	900	NR	8	0	0	NR	6 month, alive
Bodner <i>et al.</i> ^[50]	5	HRILE	147	174	NR	NR	NR	NR	NR	13	Mean = 6 month
Ruorda <i>et al.</i> ^[51]	22	HRILE	NR	180	400	2	15	14	4.5	NR	NR
Dapri <i>et al.</i> ^[52]	2	HRMKE	NR	274	NR	NR	9.5	0	0	19	1 deaths at 22 month
Espat <i>et al.</i> ^[53]	15	RTHE	NR	NR	53	1	NR	NR	NR	NR	NR
van Hillergerber <i>et al.</i> ^[54]	21	HRILE	NR	450	950	4	18	14	4.8	20	NR
Anderson <i>et al.</i> ^[55]	25	HRILE	NR	482	350	NR	11	16	0	22	Mean = 6 month
Kernstine <i>et al.</i> ^[40]	14	RMKE	300	666	400	9	22	14	0	18	87% survival, 17 month
Braumann <i>et al.</i> ^[56]	4	Hybrid	NR	60 (55-240)	NR	NR	29	NR	NR	NR	NR
Galvani <i>et al.</i> ^[57]	18	RTHE	54	267	NR	1.8	10	33	0	14	Mean = 22 month
Boone <i>et al.</i> ^[58]	47	HRILE	625	180	450	3	18	21	6.4	29	Mean = 30 month
Kim <i>et al.</i> ^[59]	21	HRMKE	109	410	150	2	21	19	0	12	All alive at 3 month
Puntambekar <i>et al.</i> ^[60]	32	HRILE	100	210	80	NR	9	9.3	NR	20	NR
Dunn <i>et al.</i> ^[41]	40	RTHE	NR	311	97	1	9	25	2.5	20	22 month median DFS
Suda <i>et al.</i> ^[61]	16	HRMKE	335	692	144	0.5	22	38	0	38	NR
Cerfolio <i>et al.</i> ^[62]	22	HRILE	~200	367	40	NR	7	4.5	0	38	100% DFS at 5 month
de la Funete <i>et al.</i> ^[63]	50	HRILE	NR	445	NR	2	9	2	0 in-hospital	19	NR
Diez Del Val <i>et al.</i> ^[64]	16	All	NR	NR	NR	NR	14	25	0	12	2 deaths, day 45 & 57
Hernandez <i>et al.</i> ^[65]	52	RILE	NR	442	NR	NR	NR	1.9	NR	NR	NR
Ishikawa <i>et al.</i> ^[66]	4	HRMKE	420	NR	NR	NR	NR	NR	0	NR	NR
Mori <i>et al.</i> ^[67]	1	RTHE	245	561	720	NR	29	0	0	40	NR
Weksler <i>et al.</i> ^[68]	11	HRMKE	NR	445	150	NR	7	9	9	19	NR
Sarkaria <i>et al.</i> ^[69]	21	RILE/RMKE	NR	556	307	NR	NR	14	5	20	NR
Coker <i>et al.</i> ^[70]	23	RTHE	NR	231	100	NR	9	8.7	4	15	Mets in 26%
Sarkaria <i>et al.</i> ^[71]	42	RILE/RMKE	NR	NR	NR	NR	NR	7 (2/30)	NR	NR	NR
Trujeda <i>et al.</i> ^[72]	18/41	HRILE	222	NR	75	NR	13	28	0	Med = 18	1 death, 2 recurrences
Puntambekar <i>et al.</i> ^[73]	83	HRMKE	NR	205	NR	1	10.4	3.6	0	18	79.5% DFS, 10 month

EBL: estimated blood loss; HRILE: hybrid robotic Ivor Lewis esophagectomy; HRMKE: hybrid robotic McKeown esophagectomy; ICU: intensive; NR: not reported; POD: post-operative day; RILE: robotic Ivor Lewis esophagectomy; RMKE: robotic McKeown; RTHE: robotic transhiatal esophagectomy; DFS: disease-free survival

Outcomes of robotic esophagectomy

Once a surgeon has mastered the robotic technique, outcomes following intervention are what truly matter. Murthy *et al.*^[27] well described the early to fairly recently-reported robotic esophagectomy series outcomes [Table 3]^[38,40,41,48-73], and the early experience at our home institution is detailed in Table 4. As the

Table 4. The DHMC experience

Patient demographics	Robotic esophagectomy, <i>n</i> = 40
Age, Mean (SD)	63.3 (8.6)
Male, (%)	36 (90.0)
Pack years, Mean (SD)	46.5 (38.5)
Smoking status, (%)	
Current	6 (15.0)
Former	24 (60.0)
Never	10 (25.0)
Alcohol status, (%)	
None	9 (22.5)
Current use ¹	19 (47.5)
Prior use ¹	2 (5.0)
Prior heavy use ²	10 (25.0)
Induction therapy, (%)	33 (82.5)
Operative time, mins, Mean (SD)	512.7 (70.2)
Length of stay, days, Median (range)	9 (5-38)
Complications ³ , (%)	
Anastomotic Leak ⁴	6 (15.0)
Pneumonia	4 (10.0)
Atrial fibrillation ⁵	6 (15.0)
Chyle leak ⁶	4 (10.0)
30-day mortality, (%)	0

¹≤ 7 drinks per week for females, ≤ 14 drinks per week for males; ²> 7 drinks per week for females, > 14 drinks per week for males; ³within 30-days of index procedure; ⁴requiring surgical intervention; ⁵requiring treatment; ⁶requiring drainage/medical treatment only. All esophagectomies were performed using either an Ivor Lewis or McKeown approach with an EEA stapler for the anastomoses in the chest and a combined stapled/handsewn approach for the neck anastomoses, respectively. Esophageal cancer was the indication for all of the esophagectomies and all patients received neoadjuvant chemoradiation with a cisplatin doublet and 54 Gy. The TNM staging ranged from T2N0M0 to T3N2M0. The procedure time was averaged between one senior surgeon (≥ 10 years of experience) and one junior surgeon (< 2 years of experience). Anastomotic leaks were addressed surgically by either stent placement or repair of the anastomosis for Ivor Lewis complications and washout of the neck for McKeown complications. DHMC: Dartmouth Hitchcock Medical Center; EEA: end-to-end anastomoses; TNM: Tumor, Node, Metastasis

number of studies presented is large, the number of experiences has also varied between the different types of esophagectomy. Detailing the IL experience, Cerfolio *et al.*^[62] originally detailed the outcomes of 22 patients who underwent robotic-assisted IL esophagectomy (also known as RAILE; note: for these cases, the abdominal phase was performed in laparoscopic fashion). A two-layer handsewn anastomosis was fashioned for 16 patients. Morbidity was minimal, 30-day mortality was 0%, and they ultimately concluded that RAILE was a safe and oncologically sound procedure^[62]. Since that time, many more have reported on their experience performing robotic IL esophagectomy^[74-81] and more recently, Nora *et al.*^[82] reviewed outcomes of RAILE. When completed by an experienced surgeon, RAILE has comparable times to esophagectomies performed via minimally invasive approaches^[28,83]. RAILE demonstrated fewer complications (wound, pulmonary, cardiovascular, and overall) compared with open IL esophagectomies and duration of hospital stay was significantly lower in the RAILE versus open cohort. However, as expected, RAILE resulted in increased pulmonary complications compared to RATE^[82]. Conversely, RATE demonstrated increased rates of major complications compared to RAILE including an increased risk of anastomotic leak, higher incidence of recurrent laryngeal nerve injuries, wound complications, and aspiration^[82].

Similar to RAILE, there were initially few reports of RATE experience in the literature. Dunn *et al.*^[41] were one of the first groups to report their outcomes in 40 patients, of which 17 had undergone neoadjuvant treatment. The operating time had a median of 311 min (range: 226-491 min), and the conversion rate was 12.5%^[41]. The morbidity rate of their cohort was high, and complications included pneumonia (20%), pleural effusion (45%), anastomotic leak (25%), recurrent laryngeal nerve injury (35%), and anastomotic stricture

(67.5%)^[27,41]. Regarding lymph node dissection, the mean \pm SD was 18.5 ± 8.7 , and the 30-day mortality was 2.5%. Interestingly, the authors reported using biologic mesh to reinforce the hiatus to address the issue of postoperative diaphragmatic hernias, a step rarely performed today^[27,41]. Others have also reported similar outcomes^[84-87]. More recently, Wecowski *et al.*^[88] prospectively reported their experience in incorporating a robotic platform for transhiatal esophagectomy. Operative duration was 334 (364 ± 108.8) min, and length of stay was 8 days. Morbidity rates were also fairly high and included respiratory failure requiring intubation (20%), pneumonia (4%), surgical site infection (11%), renal insufficiency (2%), and UTI (2%)^[88]. One patient died within 30 days secondary to cardiac arrest. The conversion rate was 9%, however none were converted in the last 25 operations and blood loss also decreased over time from an initial average of 200 cc^[88].

Kernstine *et al.*^[89] were the first to describe their completely robotic McKeown esophagectomy and three-field lymphadenectomy experience. Their series included 14 patients, of whom eight underwent a completely robotic operation^[27,89]. The anastomotic leak rate was 7%, stricture rate 14%, and average blood loss was 275 mL. Notably, the mean operating duration was 11.1 (660 min) ± 1.1 h^[27,89]. More recently, Sarkaria *et al.*^[69] described total robotic esophagectomy experience in 2012. In their cohort of 21 patients, 4 underwent McKeown esophagectomy and 17 underwent RAILE. The median operating time was 556 min and the conversion rate to an open procedure was 24%. The average blood loss was 307 mL while the mortality rate was 5%. The anastomotic leak rate was clinically significant at 14%, and two patients developed a gastrobronchial fistula secondary to a leak^[69]. Others have more recently reported their outcomes and use of various techniques with similar results^[71,90,91].

Outcome comparisons of open, minimally invasive and robotic-assisted esophagectomy

Although review of independent outcomes in robotic surgery is important, comparing open esophagectomy to minimally invasive approaches will help determine equality and/or superiority to current techniques. In looking at open versus minimally invasive procedures, Naffouje *et al.*^[92] reported their results following a propensity score-matched analysis using the NSQIP database evaluating participants who underwent OE or MIE. One hundred sixty-one OTTE patients were matched with patients 1:1 who underwent minimally invasive transthoracic esophagectomy. Higher completion rates of abdominal and mediastinal lymph node dissections were appreciated in the OTTE subgroup (26.7% vs. 3.1% and 38.5% vs. 16.1%, respectively; $P < 0.001$), and the mean operative times were also shorter (329 min vs. 414 min; $P < 0.001$)^[92]. Conversely, higher rates of wound complications were appreciated in the OTTE population (7.5% vs. 1.9%), the median hospitalization was longer (10 days vs. 8 days), more patients required discharge to a facility (18.0% vs. 8.1%), and the need for postoperative blood transfusion trended towards significance (13.0% vs. 6.8%; $P = 0.092$). They concluded the OTTE cohort demonstrated higher complication rates (46.0% vs. 33.5%; $P = 0.028$); however, there was no difference in the rates of negative margins, anastomotic leak, need for reoperation, readmission, or mortality^[92]. The results were uniformly comparable when they evaluated laparoscopic vs. robotic approaches, with the exception of higher rates of procured lymph nodes when completed laparoscopically and higher rates of mediastinal lymph node procurement when using the robotic approach^[92].

Zhang *et al.*^[93] most recently compared minimally invasive to robotic esophagectomy. They included 66 matched pairs also using propensity score-matched cohorts, finding operative time in the RAILE group to be significantly longer than that in the thoracoscopic-assisted Ivor Lewis (TAIL) group (302.0 ± 62.9 min vs. 274.7 ± 38.0 min, $P = 0.004$)^[93]. There was no significant difference in the rates of overall complications (28.8% vs. 24.2%, $P = 0.554$), blood loss {200.0 mL [interquartile range (IQR) 100.0-262.5 mL] vs. 200.0 mL (IQR 150.0-245.0 mL), $P = 0.100$ }, length of stay [9.0 days (IQR 8.0-12.3 days) vs. 9.0 days (IQR 8.0-11.3 days), $P = 0.517$], and total number of dissected lymph nodes (19.2 ± 9.2 vs. 19.3 ± 9.5 , $P = 0.955$). There were two conversions in the RAILE group, and there were no 30-day readmissions.

Chao *et al.*^[94] also performed a propensity-matched analysis evaluating lymph node procurement in robotic and minimally invasive procedures, reporting no conversion to open thoracotomy in either group and similar rates of intraoperative blood loss and the need for blood transfusions^[94]. The mean number of dissected nodes was similar in the two study groups, except for the area of the left recurrent laryngeal nerve. Notably, there was no significant difference between the RAILE and TAIL groups in regard to rates of recurrent laryngeal nerve palsy (20.6% *vs.* 29.4%, respectively, $P = 0.401$) and pulmonary complications (5.9% *vs.* 17.6%, respectively, $P = 0.259$)^[94].

Regarding direct comparison of open to robotic esophagectomy, van der Sluis *et al.*^[95,96] conducted a randomized controlled trial evaluating the robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer (ROBOT trial) in an attempt to answer this question. Notably, this study represents the only report evaluating long-term, 5-year robotic-assisted esophagectomy outcomes. This was an investigator-initiated and investigator-driven single-center randomized controlled parallel-group, superiority trial including all adult patients (age ≥ 18 and ≤ 80 years) with histologically proven, surgically resectable (cT1-4a, N0-3, M0) esophageal carcinoma of the intrathoracic esophagus who demonstrated a performance status in line with the European Clinical Oncology Group scoring of 0, 1 or 2^[95]. The percentage of overall complications (Grade 2 and higher) according to the modified Clavien-Dindo classification was the primary outcome. It started in January 2012 and patients were followed for 5 years. In total, 112 patients diagnosed with surgically resectable esophageal cancer were randomly assigned to either RAMIE or OTTE. Occurrence of surgery-related postoperative complications was the primary endpoint (designated using the modified Clavien-Dindo classification, Grades 2-5).

The RAMIE (59%) population experienced fewer surgery-related postoperative complications compared to the OTTE (80%) population (RR with RAMIE 0.74; 95%CI, 0.57-0.96; $P = 0.02$), less median blood loss (400 mL *vs.* 568 mL, $P < 0.001$), fewer pulmonary (RR 0.54; 95%CI, 0.34-0.85; $P = 0.005$) and cardiac complications (RR 0.47; 95%CI, 0.27-0.83; $P = 0.006$), and less postoperative pain (mean visual analog scale, 1.86 *vs.* 2.62; $P < 0.001$) compared to OTTE^[96]. Regarding quality of life, by POD 14, participants reported better functional recovery in the RAMIE population (RR 1.48, 95%CI: 1.03-2.13; $P = 0.038$) and the quality of life (QOL) score was better at discharge [mean difference QOL score 13.4 (2.0-24.7, $P = 0.02$)] and 6 weeks thereafter [mean difference 11.1 QOL score (1.0-21.1; $P = 0.03$)]. Most importantly, comparable oncologic outcomes were appreciated in both the short- and long-term periods at a medium follow-up (40 months)^[96].

Finally, it is important to mention the cost variations among the open, minimally invasive, and robotic techniques. Proponents of minimally invasive and robotic techniques have stated that, although they incur a higher surgical expense, this is often counterbalanced by the savings accrued through an accelerated recovery both in hospital and at home. Conversely, critics suggest that the added cost of MIE and robotic procedures is often not recovered in the postoperative period, despite the decreased or lack of ICU stay. The review of the literature supports both sides of the argument. Lee *et al.*^[97] utilized a decision-analysis model to compare the estimated costs of MIE to OE and found that, over a 1-year time period, MIE cost less than OE, with the differences mostly attributed to variations in length of stay. Others found similar findings of lower overall cost at different time points, which were also attributed to decreased postoperative costs^[98,99]. Conversely, Liu *et al.*^[100] compared MIE to OE and found that, even though the postoperative costs of MIE were significantly lower, this did not offset the higher procedural expense, as was found by other authors performing similar analyses^[101-103].

Unfortunately, there is a paucity of data comparing the cost-effectiveness of either open to robotic esophagectomies or minimally invasive to robotic esophagectomies. Ultimately, more cost studies evaluating robotic versus open and minimally invasive approaches is needed to validate the cost-

effectiveness of these techniques. More importantly, as Klapper *et al.*^[104] stated, “the onus is on our field to establish the clear cost advantages of robotic applications if we desire formal acceptance and integration into our practices”.

Discussion

Surgical treatment of esophageal cancer has evolved from an open procedure involving thoracotomy and laparotomy to minimally invasive hybrid techniques, to completely minimally invasive and/or robotic-assisted/totally robotic procedures. While the advantages of minimally invasive procedures and the needed learning curve for implementation of minimally invasive esophageal resection techniques is still not completely clear, robotic-assisted esophagectomies have consistently demonstrated lower rates of overall complications, better scores in factors related to patient satisfaction, and have produced sound oncologic outcomes. Specifically, robotic techniques result in less surgery-related and cardiopulmonary complications overall, lower postoperative pain which appeared to improve short-term quality of life, and a better short-term recovery from a functional standpoint in the postoperative period compared to OTTE^[96]. Oncological outcomes are also comparable and in line with current standards^[96]. Until the ROBOT trial, no study had specifically surveyed long term, 5-year outcomes or quality of life metrics. This information will hopefully enable more programs to consider implementation of robotic surgery for esophageal cancer operations in the future.

Nevertheless, the expense of the robotic platform and surgeon experience limit their utility in some hospital settings. Interestingly, while some have touted the needed learning curve of robotic surgery to be prohibitive to its incorporation in surgical practice (described as the longer initial operating times that eventually decrease with experience), van der Sluis *et al.*^[95,96] reported a much steeper learning curve for the robotic approach compared to the traditional MIE (e.g., laparoscopic or thoracoscopic approaches), which significantly reduces the number of surgeries needed to plateau, and may be of interest to smaller robotic centers. Most experts agree that the proctor's experience with robotic surgery and the learning surgeon's willingness to practice simulation are the most important in working to reduce the time to robotic competency.

There are several limitations for this review. First, with the exception of high-volume centers, esophagectomy in general is a procedure that is performed somewhat rarely overall. Given this, the cohorts used for comparison are often quite small. Specifically, when comparing institutional experience of MIE vs. robotic procedures, MIE has a breadth including 1000s of cases with excellent outcomes compared to the best robotic experiences, which only include 100s of cases. While MIE has certainly been tested in regards to oncologic outcomes, and lower morbidity, robotic surgery still needs to duplicate such volumes at experienced institutions to demonstrate durability. Second, there is significant breadth in the types of esophagectomy that one can perform depending on a surgeon's experience with open, laparoscopic, thoracoscopic, and robotic techniques. Furthermore, even if the same procedure is performed, there are often variations in each individual step that make comparison difficult (the use of pyloric procedures, amount of Kocher mobilization employed, use of jejunostomy tubes, *etc.*). The perioperative pathways can also significantly differ in the pre-, peri-, and postoperative setting, leading to even more variance and decrease the ability to compare different groups. There are procedural guides that can help to limit this perioperative variation, which we recommend for all surgeons, especially those just entering practice or learning new robotic techniques. Third, IL esophagectomy is the most commonly performed esophageal cancer procedure, hence most outcome metrics are based on study of this procedure type alone. While there are some data on transhiatal and McKeown techniques, this is less abundant and is often limited to small cohorts or single institution studies. Fourth, mention of the specific robotic platform used in the reporting of operating times for the robotic studies has been mostly absent. Inclusion of this detail in future reports will help surgeons understand the relatability of these results to their specific practice. Last, the

measurement of quality of life metrics has been absent from almost all studies with one exception^[105], the ROBOT trial. Ultimately, this information including complication rates and oncologic outcomes can help patients make educated decisions.

Future innovations

Clearly there is a trend towards decreasing the invasiveness of esophageal resections. As surgeons' minimally invasive skills improve, it is clear that surgical choices will steer away from hybrid procedures to either completely minimally invasive or fully robotic techniques. Additionally, technology will allow for surgeons to improve upon the most difficult portions of the procedure, advancing the overall flow of the operation. For example, the mediastinal lymph node dissection is often suboptimal in transhiatal esophagectomies given lack of direct visualization in the upper mediastinum. The need for a cervical incision in transhiatal and McKeown esophagectomies can be morbid and increasingly prone to surgical site infections given that the rest of the procedure can be performed with minimally invasive or robotic fashion. In Japan, use of non-thoracic radical esophagectomy via the transcervical and transhiatal approaches with mediastinoscopic devices has attempted to address these problems resulting in feasible surgical outcomes^[106-109]. This technique has been found to be especially helpful with squamous cell carcinoma of the esophagus, the most common histology of esophageal cancer in Japan and Asia, and often involving extensive mediastinal spread that can occur at an early age^[107]. Additionally, esophagectomy with mediastinal lymph node dissection, including the area along the recurrent laryngeal nerves, has become the gold standard for radical surgical resection, however the view achieved with standard cervical incisions has been limited^[107]. The introduction of other novel minimally invasive techniques for the lymph node dissection, such as the use of single port or robotic surgical devices, has expanded the options available to achieve improved dissection and, ultimately, better oncologic outcomes^[107]. There is no doubt that surgeons will continue to optimize all parts of the esophagectomy operation to maximally streamline aspects of the case in a minimally invasive fashion.

CONCLUSION

Today, surgical treatment strategies involving the use of open, thoracoscopic, laparoscopic, and robotic techniques are routinely used to resect and reconstruct the esophagus^[27]. However, the need to decrease the morbidity and mortality of open and hybrid surgical treatment for esophageal cancer has driven the trend towards completely minimally invasive techniques for resection, and, more recently, robotic assistance to perform esophagectomy. Robotic-assisted esophagectomy represents the newest innovation in MIE with its own unique benefits and challenges; notably, the need for specific teaching programs and proctored learning, both of which are mandatory. However, as more studies are completed which confirm the lower incidence of major complications, and similar overall and disease-free survival compared to open approaches, the use of robotic techniques to perform esophagectomy will likely become more common and work alongside other proven techniques to deliver efficient oncologic care in the least invasive fashion.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Hasson RM, Fay KA, Phillips JD, Millington TM, Finley DJ
Performed data acquisition, as well as provided administrative, technical, and material support: Hasson RM, Fay KA, Phillips JD

Availability of data and materials

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Conflicts of interest

J Phillips has previously received consulting fees from Intuitive Surgical Inc. but has no ongoing relationship. All author authors report no conflicts of interest to disclose related to this work.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Bariatric endoscopy: current primary therapies and endoscopic management of complications and other related conditions

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Abstract

The steady increase in bariatric surgery has led to room for innovation. Endoscopy has become an important tool for evaluation, diagnosis, management of complications, and even for primary bariatric interventions. Leaks are the most feared complication and new endoscopic therapies have been developed such as septotomy, double-pigtail stents, and endoscopic vacuum therapy. Additionally, primary bariatric endoscopic procedures are gaining popularity and the new procedures include intragastric balloons, stoma reduction, aspiration therapy, among others. The altered anatomy and reoperation increase the risk of complications after bariatric surgery, especially when managing conditions like achalasia, gastroparesis, and cholelithiasis. Per-oral endoscopic myotomy, per-oral pyloromyotomy, and endoscopic ultrasound-guided transgastric endoscopic retrograde cholangiopancreatography provide a less invasive approach to address these conditions. This narrative review article intends to expose current endoscopic therapies for the management of primary bariatric procedures, complications and related conditions.

Keywords: Endoscopy, bariatric surgery, septotomy, leaks, endosuturing, intragastric balloons, per-oral pyloromyotomy, per-oral endoscopy myotomy

INTRODUCTION

Each year the rise of the obesity population poses a global concern, affecting more than 600 million people worldwide^[1]. Different measures have been implemented to approach this matter and bariatric surgery



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Table 1. Summary of different areas of bariatric endoscopy innovation

Primary procedures		Management of complications		Management of concomitant conditions	
Intragastric balloons	Orbera	Leaks	Septotomy	Achalasia	POEM
	Reshape		Double-pigtail stent		
	Obalon		Endoscopic vacuum therapy		
Aspiration therapy	AspireAssist system	Weight regain	TORe ROSE	Gastroparesis	POP
Endoluminal bypass liners	Duodeno-jejunal bypass sleeve Gastro-duodenal bypass liner			Cholelithiasis	EDGE procedure
Transpyloric shuttle					
Magnetic compression gastrojejunostomy	Incisionless magnetic anastomosis system				
Mucosal resurfacing for diabetes					
Endoscopic sleeve gastropasty	OverStitch				

TORe: transoral outlet reduction; POEM: per-oral endoscopy myotomy; POP: per-oral pyloromyotomy; EDGE: endoscopic ultrasound-guided transgastric endoscopic retrograde cholangiopancreatography; ROSE: restorative obesity surgery, endolumenal

remains the most effective treatment for sustained weight loss and improvement of comorbidities^[2]. The American Society for Metabolic and Bariatric Surgery (ASMBS) reported 252,000 bariatric surgeries performed in 2018, an increase of 24,000 cases as compared to 2017^[3]. The steady increase of bariatric procedures each year has led to room for innovation. Angrisani *et al.*^[4] reported that 4% of bariatric procedures corresponded to endoluminal procedures but this percentage may be underestimated. Endoscopy has become an important tool for evaluation, diagnosis, management of complications, and even as primary bariatric interventions. Besides gastrointestinal specialists, advanced endoscopic procedures can be additionally performed by bariatric surgeons who have the knowledge and skills to perform them. Nonetheless, it is important to emphasize that management of these patients must be done in a multidisciplinary approach with enough expertise to handle these cases, which includes participation of both the bariatric and gastrointestinal specialists.

Endoscopy can be applied in various ways in bariatrics, including preoperative evaluation to study the anatomy, preoperative planning for revisions, intraoperative management to address inadvertent technical errors, postoperative management for complications, primary bariatric procedures, among other applications. With the evolution of minimally invasive techniques, endoscopy stands as an attractive alternative for the management of obesity. Bariatric endoscopy is an essential tool in the armamentarium of surgeons dedicated to the management of morbid obesity. These less-invasive endoscopic techniques serve as a promising alternative for the management of bariatric patients.

PRIMARY PROCEDURES

Bariatric surgery stands as the most effective therapy for sustained weight loss and improvement of comorbidities^[5,6]. The ever-rising epidemic of obesity has led physicians to develop non-surgical alternatives for the management of these patients. Endoscopic management of obese patients has several benefits over bariatric surgery such as the less-invasive nature of the procedures and fewer complications. A summary of available endoscopic therapies can be found in Table 1. Additionally, endoscopic techniques give the opportunity to patients who are not eligible for surgery or who prefer a less-invasive approach.

Intragastric balloons

Intragastric balloons (IGB) were first used in 1982 with the purpose of inducing a sense of satiety by a space-occupying device^[7]. Various types of IGB have been developed; however, only three of them are FDA approved, the Orbera, ReShape, and the Obalon IGB^[8]. The most common intragastric balloon used worldwide is the Bioenterics Intragastric Balloon which is made of silicone-based material and filled with

saline or air that can hold up to 400 to 800 mL^[7]. In the United States, it is sold as the Orbera Intra gastric Balloon System (Apollo Endosurgery, Austin, TX), which was approved for use in 2015^[9]. Other available balloons include ReShape (ReShape Medical Inc., San Clemente, CA) that consists of a dual balloon system. The Obalon (Obalon Therapeutics, San Diego, CA) is distinguished from the others because it is placed in the stomach by swallowing a deflated balloon in the form of a capsule, thus having a smaller capacity (250 mL)^[9].

A study evaluated the use of the Orbera intragastric balloon alone and before definite bariatric surgery over a period of 16 years. The authors reported positive short-term outcomes for the use of IGB alone, with EWL of 17.2% at 1 year; however, after 2 years weight loss was not maintained. The patients who had placement of the IGB and then underwent bariatric surgery had long-term sustained weight loss. The authors concluded that IGB should be used as a bridge therapy to definitive therapy^[10]. Moore *et al.*^[11] evaluated the outcomes at 6 months in 1,343 patients who had one or up to three Obalon IGB placed. The majority of adverse events were mild and did not require intervention; nonetheless, two severe adverse events were reported which included balloon slippage to the pylorus and gastric perforation. Although weight loss was achieved in the population studied, long-term data are still needed to prove its efficiency. The most common adverse events reported with the use of IGB are abdominal pain, nausea, vomiting, and balloon deflation^[10-12]. The use of IGB should be considered as either bridge therapy to definitive bariatric surgery or in patients who need only moderate weight loss in combination with behavior modification.

Aspiration therapy

Aspiration therapy removes up to 30% of gastric contents after a meal through a percutaneous endoscopic gastrostomy tube thus reducing the amount of chyme that reaches the small bowel for absorption^[13,14]. It should be considered in cases of severe obesity as a bridge therapy to more effective weight loss procedures. The AspireAssist System (AspireAssist; Aspire Bariatrics, King of Prussia, PA) has two components, the A-Tube and the skin-port that is attached to the tube and in the US is approved for patients with BMI of 35 to 55 kg/m² who have previously failed to lose weight with non-surgical alternatives. Four studies have been conducted to evaluate the effects of aspiration therapy on weight loss^[13]. A US pilot study comprised of 18 obese patients, compared weight loss outcomes in patients with aspiration therapy ($n = 11$) and patients with lifestyle therapy ($n = 7$) at 1 year. The aspiration therapy group lost $18.6\% \pm 2.3\%$ of their body weight versus $5.9\% \pm 5.0\%$ in the lifestyle therapy group^[15]. A multi-center, randomized, controlled trial, the PATHWAY trial, evaluated 1-year outcomes in 207 patients who had the aspiration system (AspireAssist System) placed compared to patients who had lifestyle counseling alone. The authors reported 37.2% EWL in the AspireAssist System group and 13.0% EWL in the lifestyle counseling group. Additionally, the Impact of Weight on Quality of Life score had a higher increase in the treated group across all five score measures. The majority of adverse events occurred within 7 days of the procedure and included peristomal granulation tissue, abdominal pain, nausea/vomiting, and other less infrequent events. Five serious adverse events were reported in 4 patients and consisted of peritonitis, severe abdominal pain, pre-pyloric ulcer, and A-tube replacement because of skin-port malfunction^[16]. A multicenter study conducted in Europe included 201 participants and followed them at 1, 2, 3, and 4 years after the procedure. The authors reported reduction in weight, glycated hemoglobin, triglycerides, and blood pressure. There were serious complications that included buried bumpers in 7 participants which resolved by replacement/removal of the A-Tube, and one case of peritonitis that resolved with antibiotic treatment^[17]. Although preliminary results seem promising, this device can't be applied alone for obesity management which makes it a less attractive alternative.

Endoluminal bypass liners

There are two endoluminal bypass liners that are still being trialed and yet to be FDA-approved, the gastro-duodenal bypass liner and the duodeno-jejunal bypass sleeve. Both systems create a mechanical barrier between food and the proximal small bowel, which mimic the excluded biliopancreatic limb of a Roux-

en-Y gastric bypass (RYGB)^[14,18]. The most studied of these devices is the duodeno-jejunal bypass sleeve known as the Endobarrier (GI Dynamics, Boston, MA) which is removed endoscopically 12 months after placement^[19]. Several trials have demonstrated the potential benefit of the Endobarrier for weight loss and improved glucose control. A pilot study comprised 12 patients, reported a mean %EWL of 23.6% in 12 weeks and only two patients required removal of the Endobarrier due to inappropriate device placement. Of the 12 patients included, four were diabetic and did not require their diabetes medications during the time the device was placed^[20]. A prospective trial of 42 subjects reported that the device was successfully implanted in 39 patients and they were followed up for 1 year. They reported a $19.9\% \pm 1.8\%$ reduction of total body weight loss and the EWL was $47.0\% \pm 4.4\%$ ^[21]. Although some studies have reported positive outcomes with this device, others have reported various adverse effects^[7,14]. The ValenTx (ValenTx, Inc. Carpinteria, CA, USA) is a gastro-duodenal bypass liner that is still being studied and little data exists regarding long-term outcomes. A study involving 12 patients who had the ValenTx device placed for 1 year demonstrated a mean percentage EWL of 54% but only 6 of the patients had a fully attached and functional device^[22]. Further studies and improvement of the device are still needed for the device to be approved and considered as an option for obesity.

Transpyloric shuttle

The Transpyloric Shuttle (TPS) (BARONova Inc, San Carlos, CA) is a large spherical bulb attached to a smaller cylindrical bulb through a catheter that results in delayed gastric emptying and is FDA approved. It is delivered transorally in the stomach and once it has been deployed, gastric and intestinal contractions pull the TPS into the duodenum which stops at the pylorus, causing intermittent gastric outlet obstruction and thus, delaying gastric emptying. Few studies have evaluated its safety and effectiveness. A single-center prospective, non-randomized trial of 20 patients with a mean BMI of 36.0 kg/m^2 reported a mean EWL of $31.3\% \pm 15.7\%$ at 3 months and a mean EWL of $50.0\% \pm 26.4\%$ at 6 months. The device had to be removed in two cases due to persistent gastric ulceration^[23]. A multicenter randomized sham-controlled trial in the US evaluated the safety and effectiveness of the TPS for weight loss. All patients ($n = 203$) who were treated with TPS reported an adverse event and 10/203 patients presented with a serious adverse event, no mortality was reported^[24]. These results have not yet been published but the preliminary results demonstrate that there is still a need for improvement so that it can be safely used in obese patients.

Magnetic compression gastrojejunostomy

Magnetic surgery for gastrointestinal surgery is an appealing approach that offers promising results^[25]. The Incisionless Magnetic Anastomosis System (GI Windows, Boston, MA) creates an intestinal bypass through compression of self-assembling magnets delivered endoscopically. The magnets are deployed in the proximal jejunum and in the ileum with the use of pediatric colonoscopes under fluoroscopic visualization. Once the magnets are deployed, they will couple and cause necrosis in the tissue, which leads to the formation of an anastomosis and a dual pathway. The magnets will be expelled naturally after a couple of days. Ryou *et al.*^[26] evaluated the feasibility of this device on eight pigs. By day 10, the anastomosis had already been formed and by day 90, the magnets had been completely expelled with full anastomotic patency. The first human pilot study included ten patients and used laparoscopy to confirm adequate magnet coupling. The anastomosis was created in all subjects and no device-related serious adverse events were reported. Patency of the anastomosis was confirmed at 2, 6, and 12 months. The mean total weight loss was 14.6% and the mean excess weight loss was 40.2% at 12 months. This study also showed a decrease in Hemoglobin A_{1c} and fasting glucose in diabetic patients^[27]. Even though these results sound promising, further studies and longer-term results are needed to confirm the utility of the incisionless anastomotic system.

Mucosal resurfacing for diabetes

Duodenal mucosal resurfacing (DMR) is a procedure that consists of hydrothermal ablation of the duodenal mucosa. Once the catheter is advanced into the duodenum, a balloon is inflated with heated



Figure 1. Contrast image of post endoscopic gastroplasty

water to ablate the duodenal mucosa circumferentially. This therapy has shown positive outcomes in management for diabetes^[14,28,29]. The hypothesis behind it is that through duodenal mucosal ablation, there will re-epithelialization with normal mucosa^[14]. A prospective multicenter trial showed sustained improvement of glycated hemoglobin (HbA1c) at 12 months in 37 patients with type 2 diabetes (T2D) who underwent DMR^[28]. DMR has shown improvement in glycaemic control in patients with T2D; however, the mechanisms of how glycemic control is achieved are still under study.

Endoscopic sleeve gastroplasty

The endoscopic sleeve gastroplasty is a procedure whose technique has been modified to achieve better results. The procedure is done with the use of The Overstitch (Apollo Endosurgery, Austin, TX) suturing device which was recently approved by the FDA. The procedure consists of the placement of transmural sutures in a triangular fashion such that it creates a tubular shape similar to sleeve gastrectomy [Figure 1]^[14,30]. A prospective study that included 154 patients, evaluated total body weight loss (TBWL) at 1, 3, 6, 12 and 24 months after endoscopic gastroplasty using The Overstitch (Apollo Endosurgery, Austin, TX). At 2 years of follow-up, 85.7% of patients surpassed the threshold of 25%EWL, suggested by the American Society for Gastrointestinal Endoscopy (ASGE) and the ASMBS^[30], 193 patients from 7 centers underwent endoscopic sleeve gastrectomy using The Overstitch device and were followed up at 6 months and 1 year after the procedure. There was a BMI decrease of 5 and 6 points at 6 months and 1 year, respectively. Most adverse events were mild and included nausea and emesis. Two severe adverse events were reported that required surgical intervention, one patient presented with a perigastric hematoma 1 week after the procedure and the second patient was found to have a leak 3 days after the procedure^[31]. As anatomy is not altered with this procedure, it allows for reintervention if required. This procedure has proven to be feasible with positive long-term outcomes^[30,31]; however, there has yet to be a consensus of whether this procedure should be considered over other primary bariatric procedures.

INNOVATIONS IN THE MANAGEMENT OF COMPLICATIONS

Although low in incidence, patients may present with complications after bariatric surgery. It is important to do a thorough evaluation of the patient to determine the diagnosis and advocate proper management.

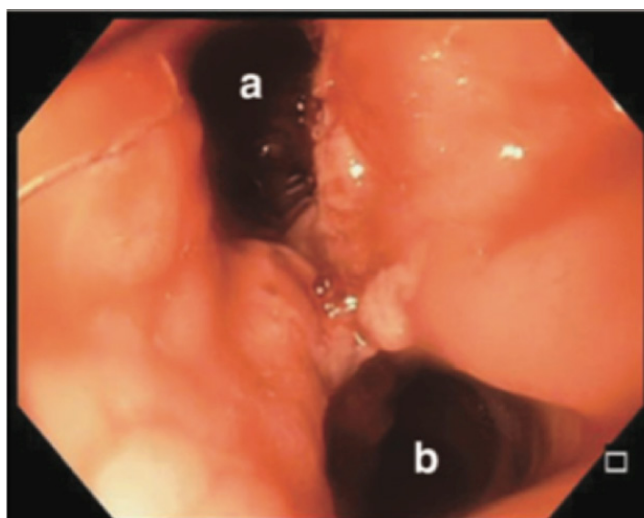


Figure 2. Endoscopic view of the septotomy completed with the abscess cavity fully exposed to the gastric lumen. (a) Abscess cavity; (b) gastric lumen

Common symptoms involve nausea, vomiting, abdominal pain, inadequate gain loss or weight regain, dysphagia, dyspepsia, reflux, increased stools, among others^[32,33]. Complications may present in the early or late postoperative period. They can present as hemorrhage, leaks, fistulas, strictures, ulcers, or erosion and their management will depend according to the type of complication. When the patients' condition is suitable, less invasive techniques are preferred. Many endoscopic procedures have been widely used over the years; however, newer devices have been recently developed.

Leaks

One of the most feared complications of bariatric surgery is the development of gastric leaks and fistulas. Even though leaks have a low incidence rate, their presentation causes a 2-fold increase in mortality and a 6-fold increase in hospital stay^[34]. In RYGB patients, most leaks arise at the gastrojejunal anastomosis, whereas in laparoscopic sleeve gastrectomy (LSG), they are usually found along the staple line^[35] and at the gastroesophageal junction^[36-38]. Leaks can be classified according to their time of presentation as acute, early, late, or chronic; presenting < 1, 1-6, 6-12, > 12 weeks after surgery, respectively^[39]. Endoscopic treatment with the use of stents, sealants, or clips has been broadly used in bariatric surgery with positive outcomes described in the literature^[40,41]. Of these, the most common used are stents. New and innovative endoscopic procedures are now available and suppose a promising alternative.

Septotomy

Abscess septotomy is a procedure utilized to control late to chronic leaks, that consists in dividing the septum formed between the abscess cavity and the gastric lumen. This allows for equalization of pressures in both cavities, favoring the drainage of the abscess cavity into the sleeve lumen [Figure 2]. Ortega *et al.*^[37] reported their experience with chronic leaks after LSG that were managed successfully with abscess septotomy in combination with aggressive dilation of the sleeve and axis rectification in order to promote distal drainage and improved management of the intraluminal pressures. Shnell *et al.*^[39] reported 10 patients with late and chronic leaks that were also effectively managed with septotomy. The authors performed on average 5 endoscopic sessions to completely resolve the leak. Nonetheless, two cases with a small perigastric cavity (< 15 mm), only needed one session to achieve leak resolution. They consider several sessions necessary to adequately drain the abscess cavity, as well as performing stricture dilation for better outcomes. This procedure represents a safe, feasible, and less invasive approach that should be strongly considered for the management of late and chronic postoperative leaks^[42-45]. In our center, we prefer

septotomy in combination with aggressive axis rectification using achalasia balloons. Septotomy procedures have better results in abscess with larger cavities. For linear abscess in which a septum dividing the lumen and the abscess cavity is small or minimal, we opt to use a pigtail catheter to control the abscess with endoluminal drainage. Unfortunately, some cases end up in esophagojejunostomy operations.

Double-Pigtail stent

Another technique available for late and chronic leaks that has gained more popularity over the recent years due to its safety, efficacy, lower cost, and good tolerance is the use of double pigtail stents. The procedure is performed by advancing a guidewire into the communicating collection under fluoroscopic guidance. Once the guidewire is in place, a double-pigtail stent is placed, which allows drainage of the abscess into the gastric cavity^[24]. A systematic review included 385 patients with gastric leak after sleeve gastrectomy that were treated with double-pigtail stents as a primary or secondary procedure. The success rate of leak resolution by using the double-pigtail stent as a first-line therapy or as a rescue therapy was 84.71% and 78.05%, respectively. The study also reported a complication rate of 13.73%, the most common being drainage migration. Furthermore, the authors conclude that this technique has proven to be efficient and well-tolerated, with the additional benefit of reducing costs by having a shorter length of stay^[24].

Endoscopic vacuum therapy

Endoscopic vacuum therapy (EVT) is a technique that is increasingly used among surgeons and endoscopists to treat leaks. The procedure consists of the placement of a sponge drainage system into the perigastric cavity, which drains the content of the leak by applying negative pressure. This system can be placed intracavitary or within the stomach lumen at the entrance to the perigastric cavity^[46,47]. Archid *et al.*^[46] reported 8 patients who developed a staple line leak following sleeve gastrectomy that were treated with EVT. The leak resolved completely in seven of the eight cases, representing an 87.5% success rate. Only one complication was reported in a patient who developed bleeding from a short gastric vessel. A study developed an online survey to evaluate the current practice of international expert therapeutic endoscopists regarding the management of upper gastrointestinal leaks. The study showed that EVT allowed for adequate drainage of the cavity and warranted granulation^[42]. One major limitation of this procedure is that the sponge needs to be replaced every 3 to 5 days^[42,47]. Nonetheless, EVT is a safe and feasible approach for leak management.

Weight regain

Weight regain or insufficient weight loss can be challenging to manage and involves a thorough multifactorial and multidisciplinary evaluation. In our center we start with endoscopic and imaging (UGI) evaluation to assess for complications. In particular, we assess for gastrojejunal dilation, pouch dilation, gastro-gastro fistulae, *etc.* All patients undergo nutritional and psychological evaluation to modify habits and behaviors. Occasionally, pharmacotherapy is added to the treatment in order to maximize success.

There are several endoscopic options to manage weight regain. The gastrojejunal anastomosis size can be reduced in order to maximize restriction. Transoral outlet reduction (TORe), aims to reduce the size of the anastomosis by placing sutures in specific locations surrounding the anastomosis. The OverStitch (Apollo Endosurgery, Austin, TX) and the EndoCinch (Bard Davol, Murray Hill, NJ) are two devices that can be used for the TORe procedure. The OverStitch has proven to be more effective for weight loss compared to the EndoCinch and is used in a similar fashion as for endoscopic sleeve gastropasty but following the TORe technique^[48]. The first technique involved placing interrupted sutures at the gastrojejunal anastomosis and the second, the creation of a pursestring. The latter resulted in greater weight loss at 12 months compared to the traditional interrupted suture pattern (19.8 %EWL with the purse-string technique *vs.* 11.7 %EWL with the interrupted technique, $P < 0.001$)^[49]. Various studies have demonstrated the safety and feasibility of this procedure. A recent study evaluated the amount of weight loss at 1, 3, and

5 years after the initial TORe in 331 post-RYGB patients who had weight regain or inadequate weight loss. The results showed that TORe is a safe, effective, and durable therapy for weight regain following RYGB^[50].

Restorative Obesity Surgery, Endolumenal (ROSE) is another available option to reduce the size of the gastric pouch and the anastomosis. The procedure consists of placement of sutures that surround the anastomosis or in the stomach wall creating plications that allow for stoma reduction. A prospective multicenter study that included 116 patients, reported that ROSE was successfully performed in 112 patients and had an average of %EWL of 18%^[51].

Strictures

Strictures after bariatric surgery represent a technical challenge. The incidence of this complication varies significantly based on different operations and different technique. Laparoscopic Roux-en-Y gastric bypass (LRYGB) has the highest incidence of anastomotic strictures ranging from 3%-27%^[52] while the incidence of stenosis after LSG ranges from 0.2% to 4%^[53]. The most common technique to treat this problem is endoscopic balloon dilation.

Dilation of gastro-jejunostomy strictures with endoscopic balloons has proven to be highly successful. In a study that included sixty-one patients, all responded to dilation without need for formal surgical revision with a 2.2% incidence of perforation^[52]. The technique involves proper identification of the anatomy and estimation of the narrowing. The diameter of commonly used diagnostic upper endoscopes ranges between 9 and 10 mm. Inability to pass the scope necessitates the use of smaller balloons, typically 6 or 8 mm. Sequential dilations can be attempted using manometric feedback. Once a maximal diameter is reached, the balloon is held in place for 1 min. We rarely exceed a diameter of 15 mm after LRYGB at our institution. Long standing strictures are less likely to resolve with endoscopic dilatation and may require operative revision.

MANAGEMENT OF CONCOMITANT CONDITIONS IN THE BARIATRIC PATIENT

Like any other patient, multiple gastrointestinal conditions may arise such as achalasia, gastroparesis, and cholelithiasis; however, their management pose a challenge for the surgeon as the anatomy is altered after bariatric surgery and reoperative fields increase the risk of complications. New endoscopic have been described and are currently taking more predominance than the surgical approach.

Achalasia in bariatrics

Obesity impacts esophageal function by altering the lower esophageal sphincter resting pressures and motility. Achalasia is an uncommon disease that could also present concomitantly after bariatric surgery. Myotomy had been the preferred therapy to treat patients with achalasia^[54]. Most recently, Inoue *et al.*^[55] introduced esophageal myotomy endoscopically instead of open surgery or laparoscopically, the procedure known as per-oral endoscopy myotomy (POEM). The therapy consists of dissection of the circular muscle bundle through a previously created submucosal tunnel at the gastroesophageal junction; after completion, the mucosal entry is closed with hemostatic clips. Symptom control after POEM is comparable to that seen with laparoscopic Heller myotomy (LHM)^[54-56]. If achalasia presents in post-bariatric patients, the management remains the same as with a normal anatomy patient. However, given that performing LHM would involve an additional operation and thus, potential increased operative risk, we consider POEM a better, non-surgical, less invasive alternative in this setting as well as for failed LHM where POEM serves as a feasible, safe, and minimally invasive technique^[57,58]. We believe that POEM should be considered as first option for managing patients with achalasia after bariatric surgery. Recently, Sanaei *et al.*^[59] explored the outcomes of POEM in 10 patients with RYGB anatomy that presented with achalasia. All patients were treated successfully, with no complications, and significant symptom improvement. Luo *et al.*^[60] also reported a case of a 67-year-old female with previous RYGB that developed achalasia and was successfully

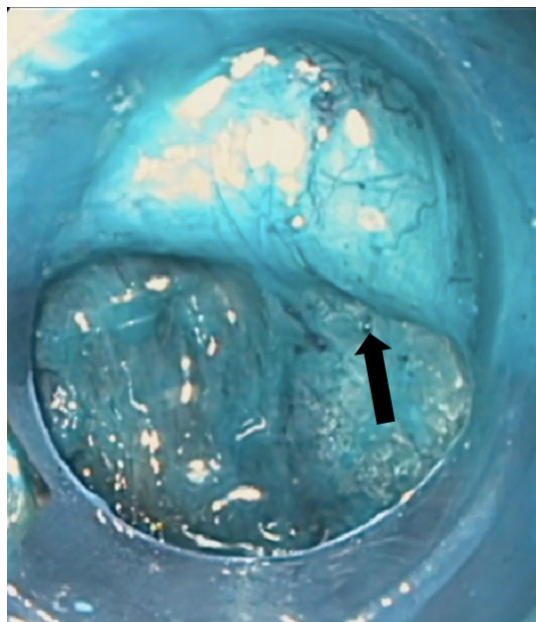


Figure 3. Endoscopic view of the pylorus. Endoscopic view of the transition between the pyloric muscle and the submucosal plain depicted by the arrow

treated with POEM. Bashir *et al.*^[54] described 6 patients with achalasia and surgical history of RYGB who underwent POEM; all but one patient had improvement of symptoms. While this procedure requires advanced endoscopic skills and more studies in obese patients are required, it shows to be a promising alternative for the management of achalasia in post-bariatric patients as it avoids manipulation of an already explored hiatus, providing greater benefit for the patient.

Gastroparesis in bariatrics

Gastroparesis is characterized by a delay in gastric emptying without a mechanical obstruction that includes a multifactorial etiology. Previously therapies used include botulinum toxin injection, endoscopic transpyloric stent placement and fixation, and laparoscopic pyloroplasty^[61]. Endoscopic per-oral pyloromyotomy (POP), also known as gastric per-oral endoscopic myotomy (G-POEM), was recently introduced as an alternative therapy for pyloric dysfunction. A mucosal lift is performed along the lesser curve of the stomach with a regular gastroscope. With an endoscopic knife, a transverse mucostomy is made after which, a submucosal tunnel is developed using the same instrument. The pylorus is then identified and divided completely [Figure 3]. Once finished, the mucostomy is closed with several endoscopic clips^[62]. It is worth mention that this procedure is more technically demanding and requires advanced endoscopic skills to perform. Rodriguez *et al.*^[63] assessed 100 patients with refractory gastroparesis that were treated with POP. Preoperatively, the mean BMI was 25.3 kg/m². Of those, 21% of the patients had a BMI > 30 kg/m². There was improvement of the Gastroparesis Cardinal Symptom Index (GCSI) score on all types of gastroparesis. Complications occurred in 10% of the patients including gastrointestinal bleeding, dehydration, capnoperitoneum, and subcutaneous emphysema. Farha *et al.*^[64] reported a case of a 43-year-old female with a history of LSG who presented with upper gastrointestinal obstructive symptoms that worsened progressively. After not responding to medical therapy or endoscopic pneumatic balloon dilation, the physicians decided to perform endoscopic per-oral pyloromyotomy. The patient was successfully treated without complications. In our experience, post-sleeve patients with gastroparesis have been safely and effectively managed with POP. Nonetheless, there is insufficient evidence in obese patients and further studies are needed.

Cholelithiasis in bariatrics

Up to 30% of patients may develop gallstones 24 months after bariatric surgery if associated with significant weight loss. The altered anatomy following bariatric surgery poses a challenge for the management of cholelithiasis. The preferred approach in these situations is laparoscopy-assisted endoscopic retrograde cholangiopancreatography (LA-ERCP)^[65]. However, this therapy requires multiple specialty team participation which may sometimes complicate the scenario. For this matter, a new endoscopic therapy was developed and can be performed by a single team with the use of an endoscopic ultrasound (EUS). The EUS-guided transgastric ERCP (EDGE) requires accessing the excluded stomach from the gastric pouch and creating a gastrogastic or jejunogastric fistula by using a lumen-apposing metal stent, after which a conventional ERCP is performed^[65,66]. Kedia *et al.*^[65] compared technical and clinical outcomes of EDGE and LA-ERCP in post-RYGB patients. The success rate for therapeutic ERCP was achieved in 96.5% and 97.7% for each group, respectively. The adverse event rate reported was 24% (7/29) for the EDGE group and 19% (8/43) for the LA-ERCP group. The events included perforation, pancreatitis, stent dislodgement, and bleeding; similar to those reported by Tyberg *et al.*^[66]. A multicenter experience using EDGE procedure demonstrated that it can be safely and effectively applied in postbariatric patients with biliary disease. Although both these studies have shown positive outcomes, prospective studies are needed to confirm its effectiveness and outcomes.

CONCLUSION

Minimally invasive techniques have progressed significantly over the past years. Management of obesity continues to expand, and multiple devices are now available to address these patients. Most of the endoscopic procedures mentioned have demonstrated positive outcomes with an adequate safety profile; nonetheless, there is still an opportunity for device improvement as well as physician expertise. It is of utter importance that bariatric surgeons are dexterous with the endoscope as it is a crucial tool to manage obese patients, not only as an adjuvant but also as a primary procedure. The utility of endoscopy for management in the obese population has increased substantially among our practice. We believe that the endoscopic approach in bariatrics is an appealing alternative to consider as first-line therapy. While there is still a need for long-term results and further progress, these new endoscopic techniques provide promising alternatives in the management for obesity.

DECLARATIONS

Authors' contributions

Made a substantial contribution to conception, design of the study, performed data analysis, and interpretation: Castro M, Guerron AD

Availability of data and materials

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Conflicts of interest

Dr. A. Daniel Guerron disclosed a financial relationship with Levita, Phenomix, Gore, Medtronic, and Biom'up. Dr. Castro declared that there is no conflict of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Minimally invasive surgical approaches to thoracic sympathectomy for hyperhidrosis

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Abstract

Thoracic sympathectomy is used for the palliation of hyperhidrosis. However, significant controversies surround the optimal surgical approach and the extent of sympathectomy. The determinants of success in the surgical palliation of hyperhidrosis are the postoperative rate of anhidrosis, recurrence of symptoms, and rate of compensatory hyperhidrosis. This paper attempts to shed light on the controversies by examining the historic background, clearly defining the anatomic considerations, and outlining the various surgical approaches culminating with robotic selective dorsal thoracic sympathectomy.

Keywords: Sympathectomy, hyperhidrosis, robotic, minimally invasive, thoracoscopic, selective sympathectomy

INTRODUCTION

Surgery on the sympathetic nervous system (SNS) is characterized by the evolution of indications and techniques that have correlated with the evolution and understanding of the physiology and anatomy of this complex part of the nervous system.

By the end of the 18th century, the anatomy of the sympathetic system was well described^[1]. However, it was over a century later that a clearer understanding of the SNS as part of the autonomic nervous system was achieved^[2]. In 1852, Bernard^[3] discovered that division of the cervical sympathetic trunk resulted in an



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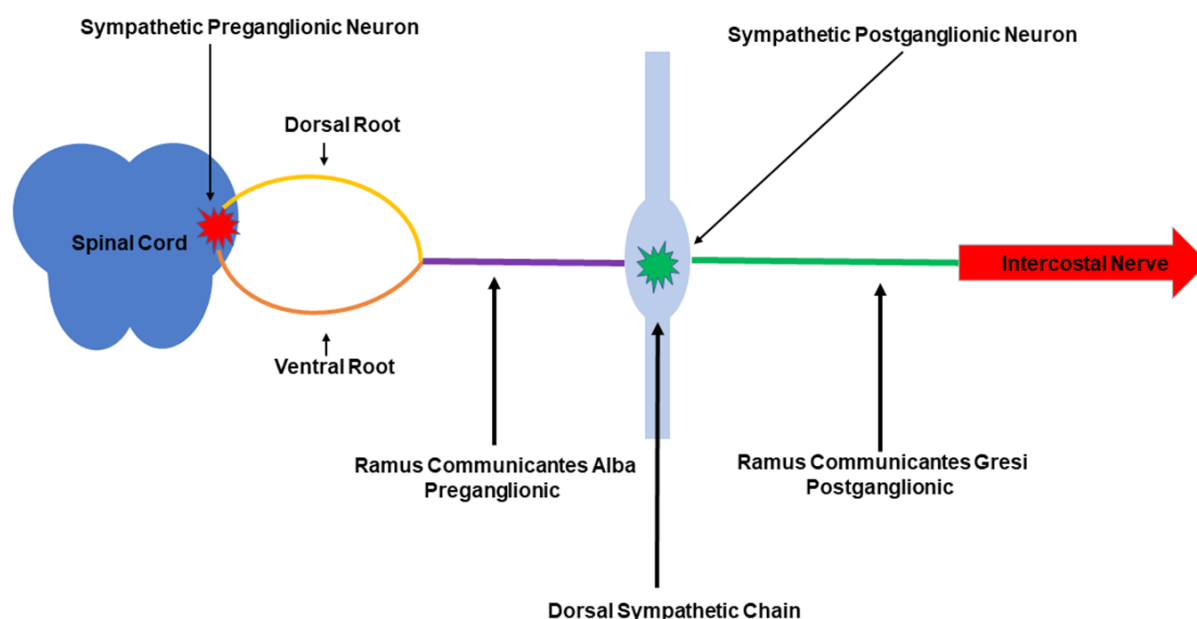


Figure 1. Sympathetic chain. Schematic representation shows the location of the first neuron in the spinal cord. Axons from the first neuron (preganglionic) travel within the dorsal and ventral roots and form the preganglionic sympathetic fibers or rami communicantes albi (white rami). Rami communicantes albi synapse with the second neuron within the sympathetic chain and the postganglionic fibers or rami communicantes grisei (grey rami) travel with the intercostal nerves

increase in the temperature of the ipsilateral side of the face. On the other hand, during the same period, Brown-Sequard^[4] noted that stimulation of the sympathetic nerves resulted in vasoconstriction. The first surgical sympathectomy was performed by Alexander^[5] in 1889 for the treatment of epilepsy. Jonnesco^[6] (1896) and Jaboulay^[7] (1900) performed cervical sympathectomy for the treatment of exophthalmic goiter. Francois-Frank^[8] advocated cervical sympathectomy for the treatment of glaucoma in 1899. In 1920, Jonnesco^[9] treated angina pectoris with sympathectomy. Leriche^[10], in 1913, and Bruning^[11], in 1923, advocated sympathectomy for Raynaud's phenomenon and other vasospastic disorders. In 1920, Kotzareff^[12] reported sympathectomy for the treatment of hyperhidrosis. The first lumbar sympathectomy was performed by Royle^[13] in 1923. Diez^[14] and Adson^[15] applied lumbar sympathectomy for ischemic lesions of the lower limbs and delineated the pathophysiology of sympathectomy. In fact, sympathectomy remained the mainstay of therapy for ischemic lesions until the advent of direct arterial revascularization in the 1960s.

In 1942, Hughes^[16] described the first thoracoscopic sympathectomy. In 1954, Krux^[17] reported 1400 thoracoscopic sympathectomies. Wittmoser^[18], a coworker of Krux, reported the single-puncture technique with the use of a special thoracoscope for sympathectomy in 1950. In fact, the studies by Wittmoser^[19] have been pivotal in the present understanding of the anatomy and the complex physiology of the dorsal thoracic sympathetic chain.

ANATOMY AND PHYSIOLOGY OF THE SYMPATHETIC CHAIN

The SNS is widely distributed throughout the body. Although afferent pathways exist and are important in relaying visceral sensory information to the central nervous system, the most clearly defined portions of the SNS are the efferent preganglionic and postganglionic fibers and their associated paravertebral ganglia.

The sympathetic chain extends from the base of the skull to the coccyx. It is located on each side of the spinal column and supplies nerves to the ipsilateral portion of the body. The sympathetic autonomic nervous system is a two-ganglion system [Figures 1-3]. The first ganglion is in the central nervous system,

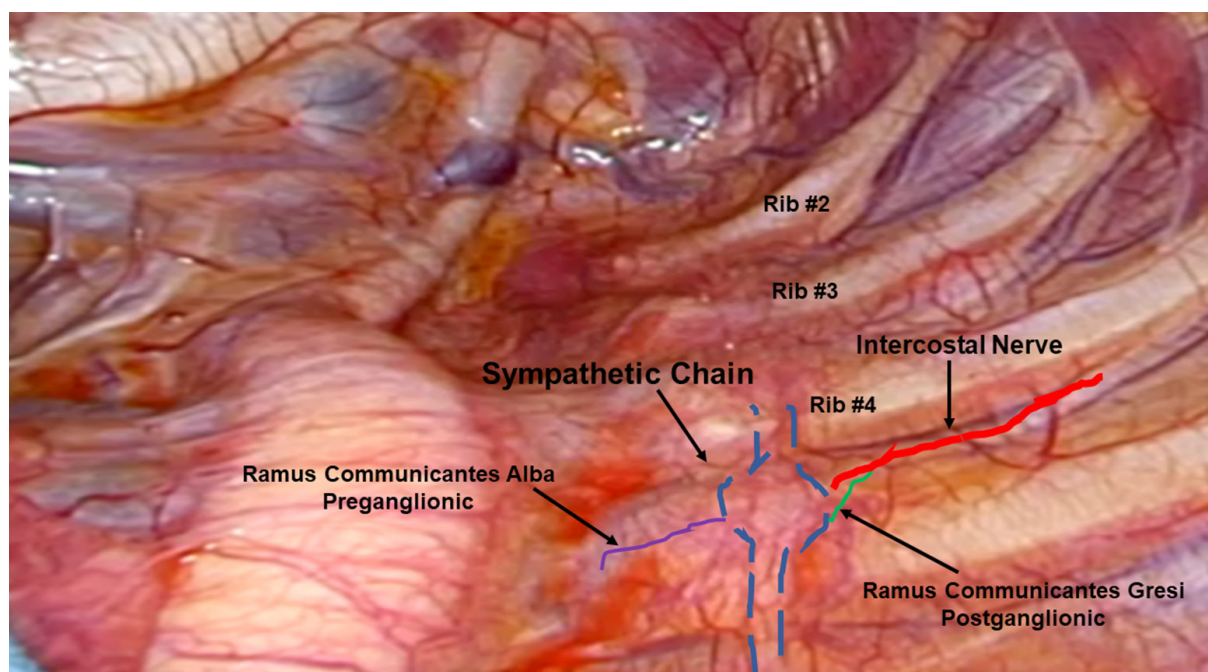


Figure 2. Thoracoscopic view of the left dorsal thoracic sympathetic chain. Axons from the first neuron (preganglionic) travel within the dorsal and ventral roots and form the preganglionic sympathetic fibers or rami communicantes albi (purple). Rami communicantes albi synapse with the second neuron within the sympathetic chain (blue), and postganglionic fibers or rami communicantes grisei (green) travel with the intercostal nerves (red). The enlarged areas (ganglia) contain both nerve bodies of the second neuron and axons from neurons at other levels

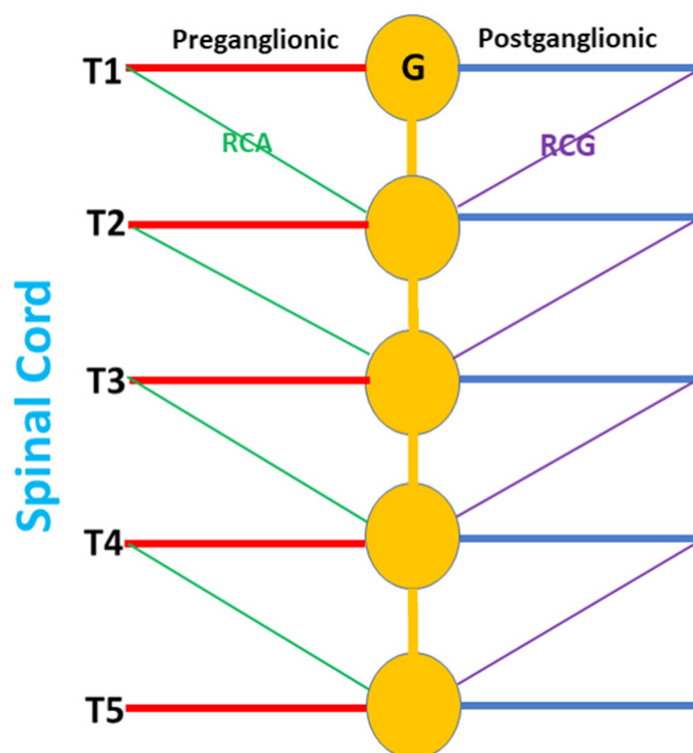


Figure 3. Schematic of the sympathetic chain for the purpose of surgical planning. RCA: rami communicantes albi; RCG: rami communicantes grisei; G: sympathetic ganglion

more specifically in the spinal cord. The cell bodies that give rise to the preganglionic fibers of the SNS lie in the intermediolateral columns of the thoracolumbar spinal cord from C8 to L2 or L3. The second ganglion is located in the sympathetic chain or in peripheral ganglia. The short myelinated preganglionic fibers which represent the axonal component of the first ganglion leave the spinal cord within the anterior nerve roots, form white rami or rami communicantes albi (RCA), and synapse with the second ganglion. In the chest, the second ganglion is in the thoracic or dorsal sympathetic chain. Axons from the second ganglion in the sympathetic chain communicate with the peripheral organs via the gray rami or rami communicantes grisei (RCG). RCG carry postganglionic fibers back to the spinal nerves for distribution to the sweat glands, pilomotor muscles, and blood vessels of the skin and skeletal muscle. Twenty-two sets of paravertebral ganglia are paired on either side of the vertebral column, connected to the spinal nerves by the white and gray rami communicantes, and interconnected by nerve trunks to form the lateral chains. They include the upper and middle cervical ganglia, the stellate ganglia (fusion of inferior cervical and T1 ganglia), and the ganglia of the thoracic, abdominal, and pelvic sympathetic trunks. Unpaired prevertebral ganglia are found in the abdomen and pelvis near the ventral surface of the vertebral column. Splanchnic nerves represent preganglionic spinal nerves from the first order ganglia which pass through the sympathetic chain without connecting with the second order ganglia in the sympathetic chain. The second order ganglia for the splanchnic nerves are the peripheral vegetative ganglia and not the ganglia of the sympathetic chain^[20]. The ganglia of the sympathetic chain are connected by the rami interganglionares (RI). The dorsal thoracic sympathetic chain is composed of sympathetic ganglia that correspond to a specific spinal segment. The dorsal sympathetic ganglia are connected by the RI. The preganglionic sympathetic nerves exit the spinal cord from the eighth cervical segment (C8) until the second or third lumbar segment (L2 or L3). Ganglia of the sympathetic chain are located at each of these segments. However, preganglionic spinal sympathetic segments not only supply the corresponding second ganglion, but they supply second ganglia located several segments above and below. Furthermore, Kuntz described the existence in some patients of an aberrant intrathoracic nerve^[21]. In these patients, the postsynaptic fibers travel with the second intercostal nerve to the brachial plexus. The C8 and T1 ganglia are fused into the stellate ganglion located above the apical pleural reflection. The stellate ganglion supplies postsynaptic sympathetic fibers to the ipsilateral face, eyelid, eyeball, and pupil. Interruption of the postganglionic sympathetic fibers from the stellate ganglion leads to Horner's syndrome. In a small percentage of individuals, the presynaptic sympathetic fibers from C8 and T1 spinal nerves travel down the RI before synapsing within the stellate ganglion. Interruption of the RI high in the sympathetic chain, even without damaging the stellate ganglion, can account for Horner's syndrome in these individuals. In addition, studies have shown that the stellate ganglion may have a greater role in the sympathetic innervation of the upper limb than has been known previously. This understanding may, in part, explain recurrence of hyperhidrosis in some individuals following thoracic sympathectomy^[22,23]. The intrathoracic ganglia of the dorsal sympathetic chain are located in the intercostal spaces. The RI traverse the proximal portion of the ribs. The second and third sympathetic ganglia supply the hand. The third, fourth, and fifth thoracic sympathetic ganglia supply the axilla. The fourth and fifth ganglia supply the skin of the abdominal wall. The lower thoracic and upper lumbar ganglia supply the lower limbs. The main effect of an upper thoracic sympathectomy is to abolish sweating of the palms and the axilla. Sympathectomy produces a vasodilatory cutaneous effect. The improved skin blood flow is on the thermoregulatory and not nutritive level. With sympathectomy, the circulation in the muscles of the upper extremity is unaltered. It seems that chronic surgical sympathectomy does not change the vascular function of the forearm. T2-T3 ganglionectomy significantly decreases pulse rate and systolic blood pressure, reduces myocardial oxygen demand, increases left ventricular ejection fraction, and prolongs the QT interval. Sympathectomy appears to decrease lung volumes as well as diffusion capacity.

Although the cause of hyperhidrosis is unknown, it is theorized to be the result of overactivity of the central nervous system. The SNS has been likened to a river emanating from central sympathetic nuclei in the brain with tributaries that emanate from the second nuclei in the periphery and carry sympathetic impulses

to the specific end organ. Sympathectomy has been likened to building a dam on the tributaries. As the flow of the central sympathetic activity remains unchanged, building a greater number of dams may cause the river to overflow through the open tributaries. This overflow of sympathetic activity through the intact sympathetic nerves, may be the analogy that best describes the condition of compensatory hyperhidrosis. In theory, by building fewer dams and allowing the flow of sympathetic activity to dissipate before building new dams, the rate of overflow in terms of compensatory hyperhidrosis may decrease. Compensatory hyperhidrosis may also dissipate. This hypothesis prompted the investigation of the role of staged bilateral selective dorsal sympathectomy.

INDICATIONS FOR SYMPATHECTOMY

Indications for sympathectomy include: intractable angina, arrhythmias, cardiomyopathy, complex regional pain syndrome, erythromelalgia, and some pancreatic and other painful abdominal pathologies, thromboangiitis obliterans (Buerger's disease), microemboli, primary Raynaud's phenomenon and Raynaud's phenomenon secondary to collagen diseases, paraneoplastic syndrome, frostbite, and vibration syndrome^[20,24]. Presently, the most common indication for thoracic sympathectomy is primary hyperhidrosis, especially affecting the palm, and to a lesser degree, axilla and face, and for facial blushing.

Hyperhidrosis results from excessive stimulation of the eccrine glands^[25]. Eccrine glands, which are present throughout the body, are most prevalent in the palms, axillae, and the plantar regions. Consequently, hyperhidrosis most commonly presents in the hands, axilla, and the feet. The upper extremity is most commonly affected, where 43% of patients have a combination of palm and axillary hyperhidrosis^[26]. In 37% of patients, hyperhidrosis is localized to the axilla and in 20% only to the hand. Hyperhidrosis is seen in 1% of the population in the West. There is a high incidence in people of Japanese ancestry and Jews of North African, Yemeni, and Balkan descent. Although most cases of hyperhidrosis are idiopathic, secondary hyperhidrosis can be the result of hyperthyroidism, obesity, anxiety disorders, menopause, carcinoid syndrome, lymphoma, pheochromocytoma, diabetes, and tuberculosis^[27].

Therapeutic options for the treatment of hyperhidrosis

A number of approaches have been advocated for the management of hyperhidrosis.

Nonsurgical management

Aluminum chloride, glutaraldehyde, and tannic acid have been used as topical agents with disappointing results.

Since the sweat glands are innervated by the sympathetic postganglionic nerves and have acetylcholine as the primary neurotransmitter, systemic anticholinergics have been advocated to block postganglionic acetylcholine receptors^[28]. Anticholinergic agents work by competitive inhibition of acetylcholine at the muscarinic receptor. Since, muscarinic receptors are present throughout the central and autonomic nervous system, the use of anticholinergics can be associated with widespread and varied side effects. Also, there are differences in the side effect profile of the different anticholinergic agents. Glycopyrrolate is a quaternary amine that has limited passage across lipid membranes such as the blood-brain barrier. Therefore, in contrast to agents such as atropine or scopolamine, which are tertiary amines and can easily penetrate lipid barriers, glycopyrrolate has fewer central nervous system side effects and may have less effect on the heart rate at lower doses^[29]. Glycopyrrolate, oxybutynin and methantheline bromide are the most commonly used anticholinergics for the treatment of hyperhidrosis^[30]. The most common side effect is dry mouth due to inhibition of salivary glands. Other side effects include: constipation, nausea, vomiting, bloating, loss of taste, mydriasis, cycloplegia, dry eyes, blurred vision, photophobia, reduced phlegm, urinary retention, erectile dysfunction, loss of libido, arrhythmias, headache, dizziness, insomnia, drowsiness, confusion, seizures, pruritus, and urticaria. In addition, concurrent use with other medications

with anticholinergic activity such as phenothiazines, antiparkinsonian drugs or tricyclic antidepressants, intensify the antimuscarinic effects and can increase side effects. Relative contraindications to the use of anticholinergics drugs are: glaucoma, obstructive uropathy, obstructive diseases of the GI tract, paralytic ileus, severe ulcerative colitis, and myasthenia gravis.

Beta blockers have been used to improve symptoms of social phobias and performance anxiety^[31].

Calcium channel blockers have also been used. The success of these techniques has been short-lived and limited.

Iontophoresis which attempts to coagulate eccrine glands by the use of electrical current has been used for palmar and plantar hyperhidrosis. This technique has had limited success^[32,33].

Botulinum toxin injection is the most studied hyperhidrosis treatment and demonstrates consistent improvement in Hyperhidrosis Disease Severity Scale (HDSS) scores and in sweat production as measured in the axillae and palms^[34,35]. It may be considered first- or second-line therapy for hyperhidrosis affecting the axillae, palms, soles, or face. Botulinum toxins bind synaptic proteins, blocking the release of acetylcholine from the cholinergic neurons that innervate the eccrine sweat glands. The most commonly used preparation is onabotulinumtoxinA (Botox). OnabotulinumtoxinA is administered intradermally in the affected area. In most cases, treatment results last six to nine months. Adverse effects typically include injection-site pain and bruising, decreased grip strength when injected into the palms, and frontalis muscle weakness when used on the forehead.

A newer, noninvasive local treatment of axillary hyperhidrosis uses microwave technology^[36]. The application of microwave energy destroys eccrine sweat glands by creating local heat, resulting in cellular thermolysis. This outpatient procedure is applied with a handheld transducer after mapping the axillae using a starch-iodine test. Local anesthesia is required. This treatment results in a decrease in the HDSS score of at least one point in 94% of patients and at least two points in 55% of patients^[37].

Fractionated microneedle radiofrequency is another emerging treatment in axillary hyperhidrosis^[38]. During this procedure, microneedles are placed 2 to 3 mm under the skin, and radiofrequency energy is applied. This therapy results in a decrease in the HDSS score of at least one point in nearly 80% of patients^[39].

Alternative surgical therapies

Surgical alternatives such as resection of the axillary sweat glands or subcutaneous curettage have been limited only to axillary hyperhidrosis. However, these techniques have had little acceptance due to the highly invasive nature of the procedures and the high complication rates and high relapse rates several months after the procedure^[40,41].

Dorsal thoracic sympathectomy

Nonsurgical methods for accomplishing dorsal thoracic sympathectomy have included: (1) percutaneous injection of phenol; (2) CT-guided injection of phenol; and (3) percutaneous radiofrequency thermal ablation^[42-45]. These techniques have been hampered by very high recurrence rates shortly after the procedure. Dorsal sympathectomy has been the only treatment for hyperhidrosis that has resulted in long-term success.

Many surgical approaches have been described for dorsal thoracic sympathectomy. These have included: (1) the posterior thoracic approach; (2) cervical supraclavicular approach; (3) transthoracic approach; (4) transaxillary approach; (5) thoracoscopic approach; and (6) robotic thoracoscopic approach.

Posterior thoracic approach: The classic posterior thoracic approach was popularized by Adson and modified by White^[15]. This approach required partial rib resection and resulted in prolonged painful recovery.

Cervical supraclavicular approach: Telford devised a supraclavicular approach^[46]. Although this approach obviated the pain associated with the rib resection, it was technically demanding and associated with complications. The transcervical route requires attention to the highly complex anatomy of the cervical region, and the complications are associated with injury to these structures. The advantages of this approach include the ability to perform a bilateral sympathectomy in one sitting, minimal pain, and good cosmetic results. With this approach, due to the inability to reach the lower portion of the sympathetic chain, the T4 ganglion cannot be excised. Therefore, this approach is not as efficacious for patients experiencing axillary hyperhidrosis.

Transthoracic approach: Goetz, Marr, and Palumbo advocated an anterolateral transthoracic approach^[27]. Although this approach provided the best exposure and the most accurate sympathectomy possible, this technique did not gain popularity due to the significant morbidity associated with a thoracotomy.

Transaxillary approach: In 1954, Atkins^[47] described a transaxillary approach which became popular and is even used in some centers today. As has been noted, this technique suffers from the shortcoming of pain and lack of visualization through a very small transaxillary incision.

Thoracoscopic approach: The thoracoscopic approach to dorsal sympathectomy was used as far back as the 1940s. With the advent of advances in optics, lighting, and video endoscopic instrumentation, video-assisted thoracic surgery became the standard approach to dorsal sympathectomy^[48,49]. Presently, there are four video-assisted approaches to enable dorsal thoracic sympathectomy.

Classic resection: This technique (ganglionectomy) [Figures 2 and 3] involves the resection of the entire sympathetic chain including the T2, T3, and T4 sympathetic ganglia with the intervening RI.

Clipping of the sympathetic chain: Proponents of this technique have emphasized the potential reversibility of the removal of the clip. However, clip removal has not been necessarily associated with recovery of sympathetic function^[50]. Furthermore, some authors have postulated that clips may contribute to postoperative neuralgia^[27,51].

Thermal ablation of the dorsal sympathetic ganglion: This technique which can be accomplished using conventional electrocautery, diathermy with monopolar precise coagulation, or radiofrequency ablation has become the most commonly used technique^[51]. The proponents of this technique have emphasized the ease of use, shorter operative times, the ability to perform bilateral sympathectomy, and the minimally invasive nature of the procedure. However, in a meta-analysis of published studies of thoracoscopic sympathectomy for hyperhidrosis, Hashmonai *et al.*^[51], showed that resection achieved superior results. It is due to the complex nature of the resection even with modern conventional video-assisted thoracic surgical techniques that the majority of surgeons choose thermal ablation of the sympathetic chain.

In 2011, the Society of Thoracic Surgeons expert consensus report for the treatment of hyperhidrosis was published^[52]. This report was based on 1,097 published articles in the world's literature on hyperhidrosis from 1991 to 2009. These studies suggested that primary hyperhidrosis of the extremities, axillae or face is best treated by endoscopic thoracic sympathectomy. Interruption of the sympathetic chain could be achieved either by electrocautery or clipping. This report emphasized the need for the adoption of an international nomenclature that would refer to the rib levels (R) instead of the vertebral level at which

the nerve is interrupted, and how the chain is interrupted, along with systematic pre- and postoperative assessments of sweating pattern, intensity and quality of life. This report suggested that the highest success rates occur when interruption is performed at the top of R3 or the top of R4 for palmar-only hyperhidrosis. R4 may offer a lower incidence of compensatory hyperhidrosis but moister hands. For palmar and axillary, palmar, axillary and pedal and axillary only hyperhidrosis, interruptions at R4 and R5 are recommended. The top of R3 is best for craniofacial hyperhidrosis.

EXTENT OF SYMPATHECTOMY

The success of dorsal thoracic sympathectomy is judged by: (1) High rate of relief of hyperhidrosis; (2) low rate of recurrence; and (3) low rate of compensatory hyperhidrosis and gustatory hyperhidrosis.

Invariably, the surgical procedures achieve symptomatic relief but are associated with compensatory hyperhidrosis in 50%-97% of patients^[53-56]. Compensatory hyperhidrosis that occurs on the trunk and lower extremities following sympathectomy and gustatory hyperhidrosis, which refers to facial sweating associated with eating or olfactory sensation of hot spicy food, are significant complications of sympathectomy. As a result, several studies have attempted to determine whether limiting the extent of sympathectomy can impact the incidence of these two complications^[57-64]. However, the results have been inconsistent, and randomized trials have not been performed. In 2000, Furlan *et al.*^[65] reviewed published series after sympathectomy. They reported a compensatory hyperhidrosis rate of 52.3%, gustatory hyperhidrosis rate of 32.3%, phantom hyperhidrosis of 38.6%, and Horner's syndrome in 2.4% of patients. In 2200 patients undergoing ablation of T2 ganglion for palmar sweating and T3-4 ganglia for axillary sweating, Lin and associates showed successful sympathectomy in 99% of patients^[66]. However, compensatory hyperhidrosis was noted in 88% of patients. It is important to note that the rate of compensatory hyperhidrosis depends on the rigor by which compensatory hyperhidrosis is defined. If compensatory hyperhidrosis is defined as "any increased amount of new sweating", as has been defined in many of the aforementioned studies, the rate of compensatory hyperhidrosis is very high. On the other hand, if some new compensatory sweating is tolerated by the patient and compensatory sweating is defined as "sweating that cannot be tolerated", the rate of compensatory hyperhidrosis will be much lower. The latter scenario is consistent with the experience of many surgeons. However, for the purpose of clarity and comparison of different surgical techniques, it is best to define compensatory in the most rigorous manner.

From these studies, a number of conclusions can be reached: (1) longer extent of dorsal thoracic sympathectomy is associated with greater risk of compensatory hyperhidrosis; (2) the severity of compensatory hyperhidrosis is decreased with staging of dorsal sympathectomy with unilateral sympathectomy accomplished a few weeks apart versus bilateral sympathectomy at the same setting; (3) the extent of compensatory hyperhidrosis is decreased with selective ramicotomy; and (4) incidence of Horner's syndrome is lower with transthoracic approach when sympathectomy is performed by dissection versus diathermy of the T2 ganglion or when sympathectomy is limited to below the T2 ganglion.

Landmark studies by Wittmoser^[18] and later by Friedel^[20] have determined the ideal extent of sympathectomy.

It has been postulated that limiting the extent of sympathectomy or sympathicotomy may decrease the rate of compensatory hyperhidrosis. The thoracic sympathetic chain is composed of both nerve bodies of the second sympathetic neuron as well as postganglionic axons from nerve bodies from other levels that travel within the chain. Microscopic examination of what macroscopically appears as a ganglion in the sympathetic chain reveals a combination of nerve bodies as well as communicating axons from other nerve bodies that travel up and down the chain. Based on this understanding, division of a single macroscopic ganglion does not result solely in the removal of the nerve bodies to that specific level, but in addition,

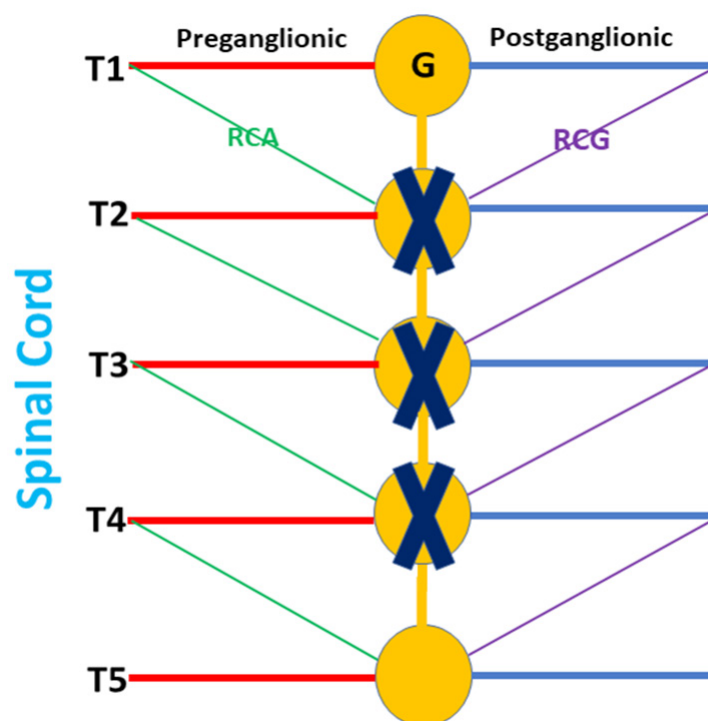


Figure 4. Classic gangliectomy as depicted by resection of the sympathetic chain and ganglia (X) from T2 to T4. RCA: rami communicantes albi; RCG: rami communicantes grisei; G: sympathetic ganglion

results in the division of the axons from nerve bodies from other levels that travel through the chain. This realization may explain the variability of the extent of sympathectomy when the chain is divided, or specific macroscopic ganglia are removed.

The extent of sympathectomy correlates with the incidence of complications. Disruption of the chain (sympathectomy), or parts of the chain (sympathicotomy) or removal of selected ganglia will result in disruption of sympathetic activity to more than just the upper extremity. Only division of the postganglionic fibers that emanate from the chain and join the intercostal nerves, 2, 3 and 4, can assure selective disruption of sympathetic activity to the upper extremity. However, the efferent or postganglionic fibers at times travel behind the chain before emerging laterally to join the intercostal nerve. Therefore, to assure division of all the postganglionic fibers that travel with intercostal nerves 2, 3 and 4 to the upper extremity, the entire chain needs to be skeletonized and elevated away from the chest wall.

Selective postganglionic sympathectomy represents a more directed approach to sympathetic denervation of the upper extremity^[67]. In this procedure, the sympathetic trunk and ganglia are left intact and only the rami that accompany intercostal nerves 2, 3 and 4 to the upper extremity are divided selectively.

Friedel *et al.*^[26] studied three possible techniques for selective sympathectomy: (1) thoracic resection of the sympathetic chain including T2, T3 and T4 ganglia and intervening IR. They referred this technique to as interganglionare. They concluded that this technique results in compensatory hyperhidrosis in the majority of patients. With this technique, Horner's syndrome is seen in a smaller percentage of patients compared to thermal ablation. The shortcoming of this technique is the possibility of leaving the postganglionic RCG with less than complete sympathectomy [Figure 4]; (2) division of the preganglionic RCA, while leaving the sympathetic chain intact [Figure 5]; and (3) division of postganglionic RCG for T2 to T4, while leaving the sympathetic chain intact [Figure 6].

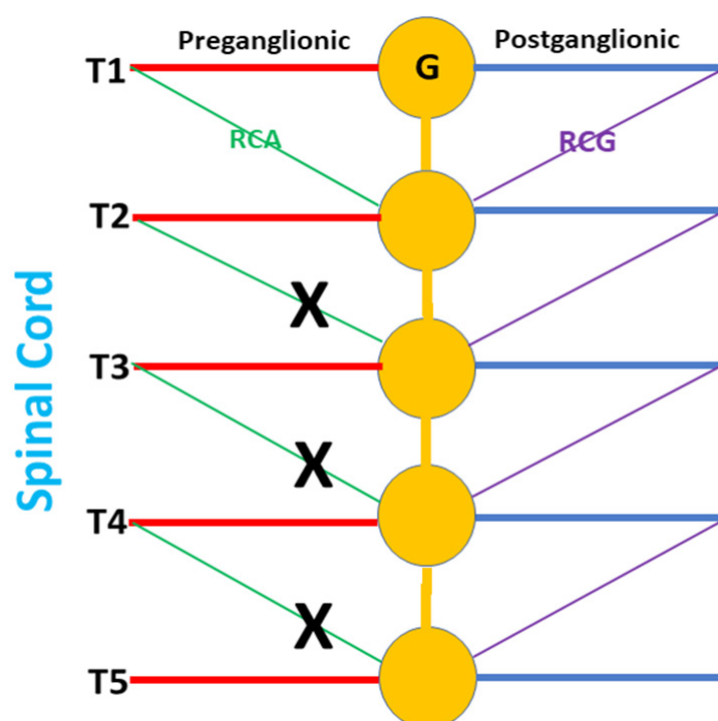


Figure 5. Preganglionic sympathectomy as depicted by division of the RCA from T2 to T4. The sympathetic chain is left intact. RCA: rami communicantes albi; RCG: rami communicantes grisei; G: sympathetic ganglion

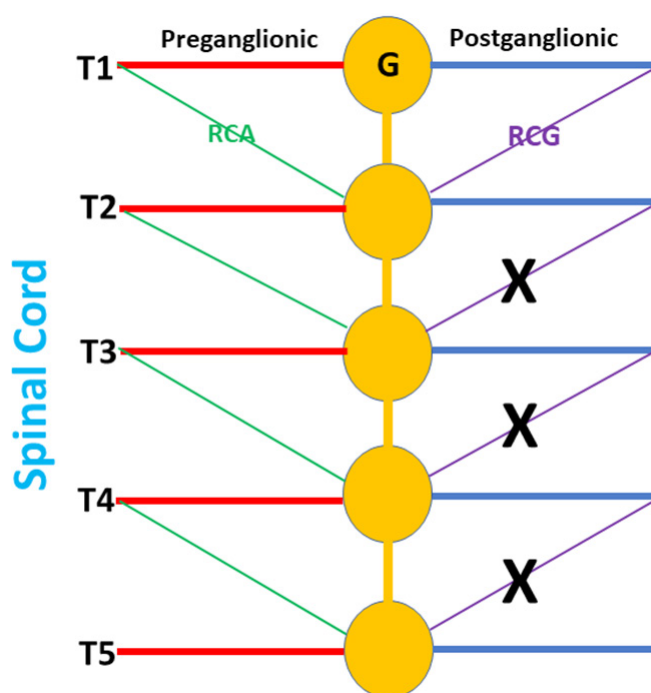


Figure 6. Postganglionic sympathectomy as depicted by division of the RCG from T2 to T4. The sympathetic chain is left intact. RCA: rami communicantes albi; RCG: rami communicantes grisei; G: sympathetic ganglion

Using the technique of selective sympathectomy with the division of the postganglionic RCG for T2 to T4, these authors showed a 95% reduction in perspiration and a compensatory hyperhidrosis rate of

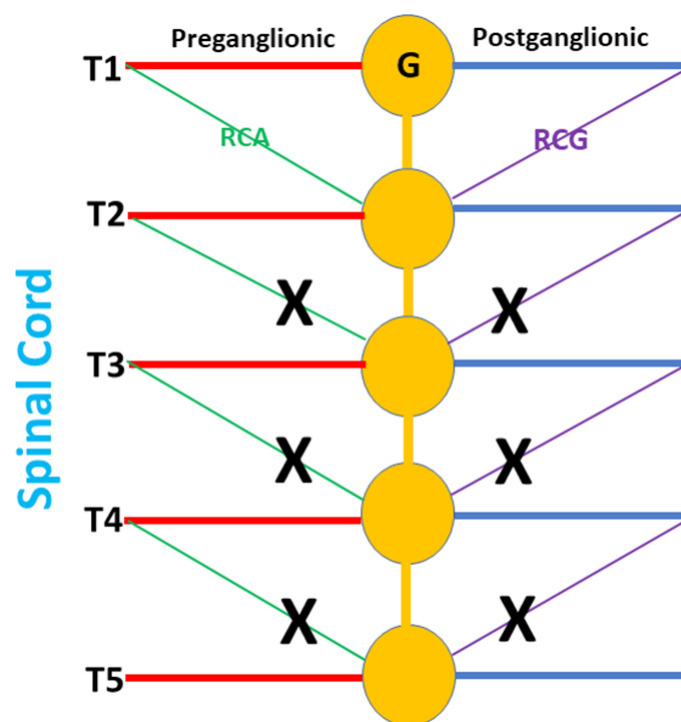


Figure 7. Selective dorsal sympathectomy as depicted by division of both the RCA and RCG from T2 to T4. The sympathetic chain is left intact. RCA: rami communicantes albi; RCG: rami communicantes grisei; G: sympathetic ganglion

2.5%^[20]. Furthermore, with this technique, they did not report any patients with Horner's syndrome. Finally, this technique has resulted in the lowest reported rate of compensatory hyperhidrosis (16%). However, subsequent studies with longer follow-up, showed that the results for reduction of perspiration were transient and that the long-term compensatory hyperhidrosis rate with this technique was 60%-70% and was comparable to other techniques. It has been suggested that the lack of sustained results with this technique was the result of poor visualization of the rami and incomplete ramicotomy as the preganglionic rami were left intact.

Using robotic technology and taking advantage of the 3-dimensional high-resolution magnified view and improved instrument maneuverability in the confined space, Coveliers and colleagues reported a series of patients who underwent simultaneous bilateral selective dorsal sympathectomy. In these patients, the preganglionic and postganglionic rami as well the communicating rami posterior to the sympathetic chain were divided and the sympathetic chain was left intact [Figure 7]. These authors used anhidrosis rather than reduction of perspiration as an endpoint. After two years follow-up, there was a 96% rate of anhidrosis and a 7.2% rate of compensatory sweating^[68,69].

As compensatory hyperhidrosis after sympathectomy is believed to result from redirection of sympathetic activity to other parts of the body, and has been shown to be related to the extent of sympathectomy, Gharagozloo *et al.*^[70] hypothesized that staged bilateral robotic sympathectomy of one upper extremity followed by the other may result in even lower levels of compensatory hyperhidrosis. Gharagozloo *et al.*^[70] studied robotic staged bilateral selective sympathectomy (RSS) directed at the division of the preganglionic and postganglionic rami without interruption of the sympathetic chain. During RSS, the preganglionic and postganglionic sympathetic fibers and communicating rami to intercostal nerves 2, 3, and 4 were divided. The sympathetic chain was left intact [Figure 7]. Anhidrosis was used as an endpoint and was seen in 98% of patients. In turn, compensatory hyperhidrosis was defined rigorously as "any new sweating". At a mean follow up of 28 ± 6 months, 46/47 (98%) patients were free of sustained compensatory hyperhidrosis.

ROBOTIC SELECTIVE DORSAL SYMPATHECTOMY

One of the shortcomings of the VATS techniques stems from the fact that the instruments are introduced through ports or small incisions which amount to holes in the chest wall. The instruments pivot at the entry holes and can be moved in four directions. The limited mobility of conventional endoscopic instruments, whether in the abdomen or the chest, has been referred to by some investigators as “chopstick surgery”. The chopstick nature and the limited maneuverability of the effector instruments stems from the rigid shaft access fixed to the thorax by the entry hole. This technical shortcoming limits the surgeon in performing fine dissection and complex three-dimensional maneuvers. Pivoting instruments on the chest wall results in a large radius of curvature for the tip of the instrument and makes fine dissection in deep spaces such as the mediastinum very difficult and even dangerous.

Another shortcoming of the VATS technique is in the lack of the three-dimensional visualization. The surgeon has to use two-dimensional information from the video monitor to create a three-dimensional mental image. This fact requires significant experience and can prove to be a course of fatigue for the surgeon. Most importantly, using such indirect means of judging depth perception is rarely equivalent to binocular vision. In maneuvering the sympathetic chain away from the underlying vessels and determining the position of the RCG, binocular vision is paramount. The use of robotic technology obviates these difficulties. The Da Vinci robot (Intuitive Surgical) represents an ideal tool for the accurate dissection of the sympathetic chain away from the underlying vessels and identifying the preganglionic and postganglionic fibers to perform highly selective dorsal sympathectomy. The indispensable features of the Da Vinci robot for performing this procedure are: (1) the EndoWrist or the cable-driven wrist at the end of the robotic arm. The placement of the robotic arm through the VATS hole is comparable to and accomplishes the chopstick maneuvers performed by conventional VATS instruments. However, the EndoWrist at the distal end of the robotic arm is positioned in the confined spaces within the chest and brings 4_ more of freedom and six additional directions of movement compared to normal VATS techniques. The EndoWrist provides the surgeon with fine instrument maneuverability in a very confined space; (2) the Da Vinci robotic system is designed to provide downscaling from the motion of the surgeon's hand to that of the robotic instrument. This is invariable in dissecting fine and fragile intrathoracic structures. Furthermore, a 60 Hz motion filter is used to filter out any tremor in the surgeon's hand; and (3) the binocular robotic camera provides superb three-dimensional visualization by the nature of being mounted on the central robotic arm. It can be manipulated by the surgeon. The surgeon's ability to manipulate the camera and the arm recreates the natural biologic motion of the surgeon's head, eyes, and hands in providing optimal hand-eye coordination.

Operative technique

Room setup is depicted in [Figure 8](#). Room setup is the same for both right- and left-sided procedures.

Anesthesia

Patients require single-lung ventilation. We prefer a left-sided double-lumen endotracheal tube to a bronchial blocker. In our experience, bronchial blockers are prone to dislodgment during the surgical procedure and require frequent manipulation which is difficult while the robot is in position. In addition, selective sympathectomy requires very precise dissection and a controlled visual field without intrusion from the inflating lung. Longer tubing is required during the robotic procedure as the anesthesiologist will occupy a more remote position away from the patient. The patient is placed in a full lateral decubitus position. We prefer to perform highly selective sympathectomy beginning with the most affected side, returning after any compensatory hyperhidrosis has subsided or plateaued in severity. The table is flexed to open the intercostal spaces and the position of the double-lumen tube is reconfirmed after final positioning. The patient then is prepared and draped in a routine manner. The superior portion of the drape is allowed to cover the patient's head. After port placement, the table is unlocked and rotated 30 degrees from its normal position to facilitate the positioning of the robot over the patient's head.



Figure 8. Room setup. The room setup is the same for right- or left-sided approach

The surgeon stands facing the patient's back. Pleural entry is with a Hassan needle. Saline is infused and care is taken to look for easy egress of the saline from the needle. If there is any question of pleural adhesions, we use a Visiport Instrument (Medtronic Inc. Norwalk, CT) for entry into the pleural space under direct vision. A line is drawn from the tip of the scapula to the costal arch. This corresponds to the midaxillary line. Port #1, the camera port (#1) is placed in the sixth intercostal space in the midaxillary line [Figures 9-11]. Port #2, 8-mm trocar (#2) is placed in the third intercostal space in the anterior axillary line. For approach to the sympathetic chain in the right chest, this port will be used by the right robotic arm, and for the left-sided sympathetic chain, this port will be used by the left robotic arm. Port #3, 8 mm, (#3) is placed in the fifth intercostal space posterior axillary line. For approach to the sympathetic chain in the right chest, this port will be used by the left robotic arm, and for the sympathetic chain in the left chest, this port will be used by the right robotic arm. An Auxiliary (AP) 2 cm incision is made in the sixth intercostal space in the anterior axillary line. A retractor (Endopaddle Retract, Medtronic Inc., Norwalk, CT. USA) is passed through this port and used to retract the lung medially. The retractor is attached to the operating table by a self-retaining system (Mediflex, Velmed Inc., Wexford, PA, USA). Carbon dioxide insufflation is not used. At this point, the robot is brought into the operating field over the patient's head. The camera arm with a 30-degree down-viewing binocular camera is introduced through port #1. In the right chest, the right robotic arm with the robotic hook cautery is positioned through port #2, and the left robotic arm with the robotic DeBakey forceps is positioned through port #3. In the left pleural space, the right robotic arm enters the pleural space through port #3 and the right robotic arm enters the pleural space through port #2 [Figure 12]. The sympathetic chain is identified. The ribs are counted, electrocautery marks are placed away from the sympathetic ganglia to specify the position of ganglia #2, #3, and #4. The portion of the sympathetic chain between ganglia #4 and #5 overlying rib #5 is identified, dissected with the hook cautery. The sympathetic chain is encircled and lifted with a rubber atraumatic vascular loop. The postganglionic fibers (RCG) can be identified easily as the fibers emanating from the chain towards the distal portion of the ribs. These fibers are divided using electrocautery. The preganglionic fibers entering the sympathetic chain are also divided and the chain is elevated. Dissection is carried to the level of the second sympathetic ganglion. Following the division of the preganglionic and postganglionic fibers, the

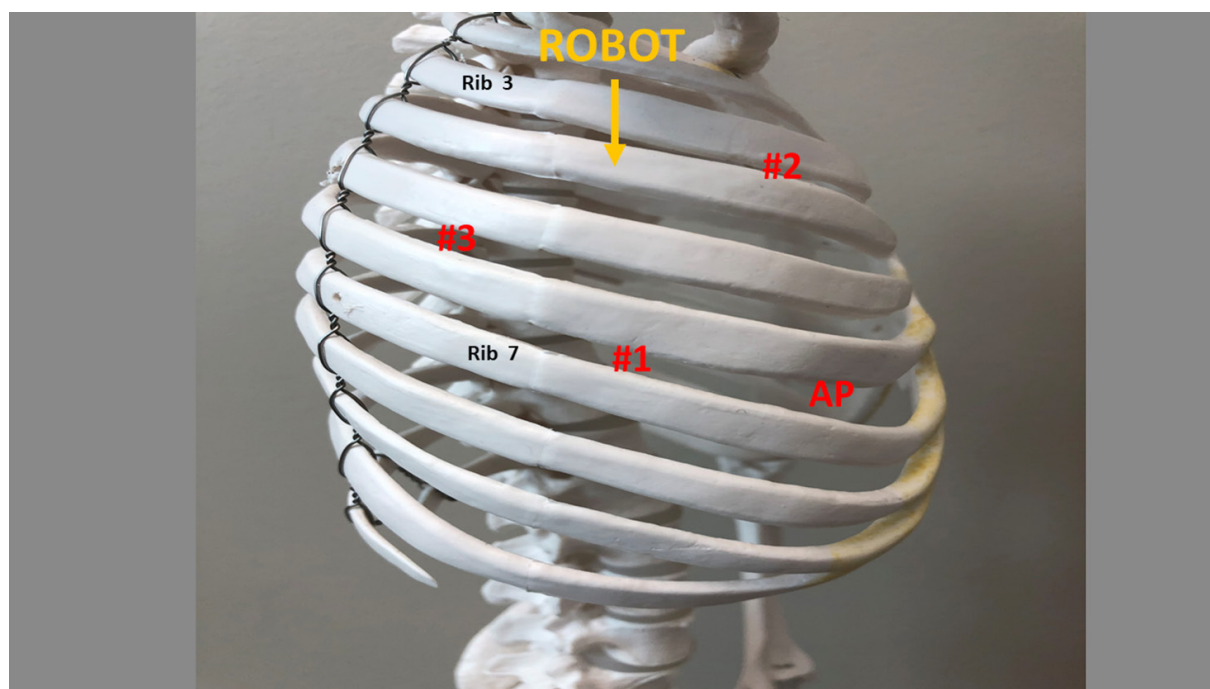


Figure 9. Schematic depicting port placement during robotic selective dorsal sympathectomy. Right chest. AP: accessory port

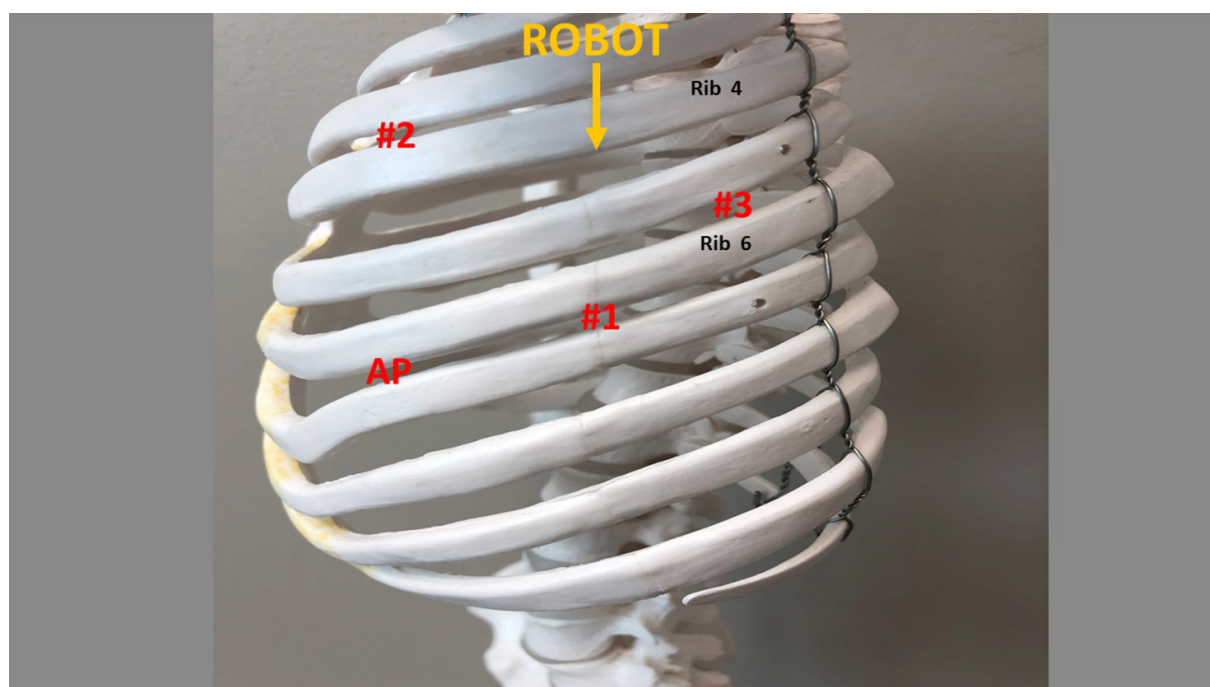


Figure 10. Schematic depicting port placement during robotic selective dorsal sympathectomy. Left chest. AP: accessory port

sympathetic chain is elevated and all posterior attachments to the ribs are severed using electrocautery. This maneuver disconnects the RI which are communicating fibers between the ganglia. Following completion of the highly selective sympathectomy, flexible drain is positioned posteriorly in the pleural space and brought out through the AP. On-Q subpleural catheters are placed traversing T2 to T8^[71]. All patients are extubated and are returned to the recovery room.

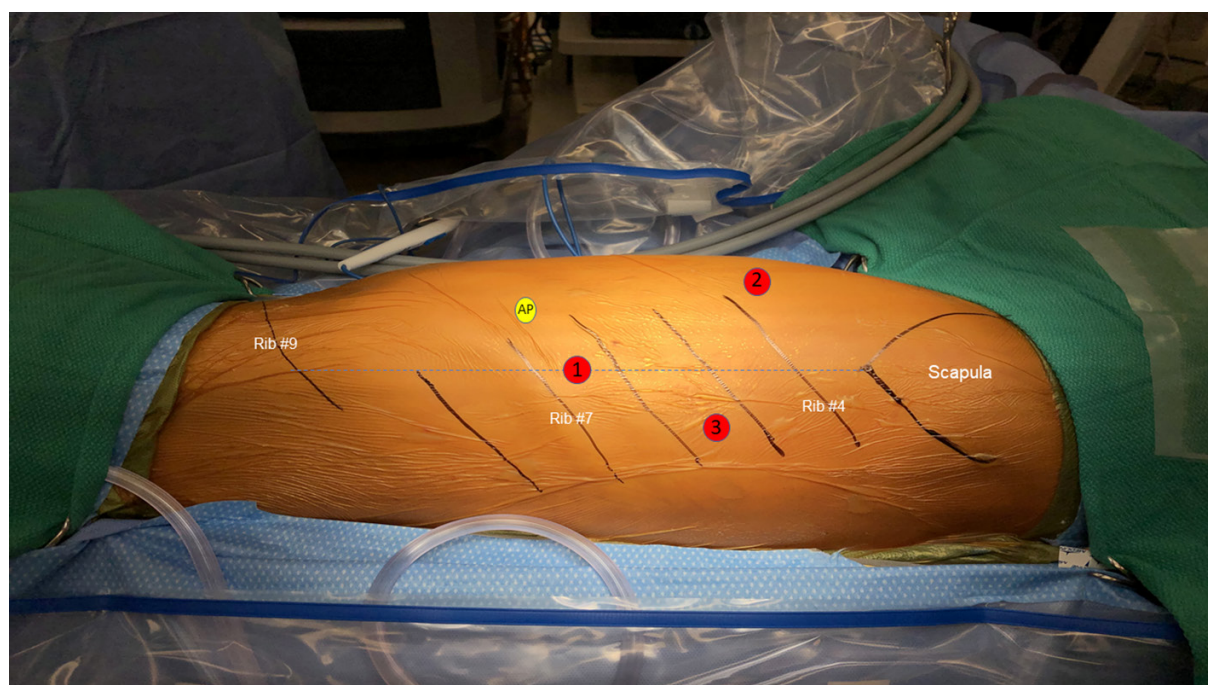


Figure 11. Patient undergoing left selective dorsal sympathectomy. Pt is in a decubitus position. A line is drawn from the tip of the scapula to the costal arch. This denotes the midaxillary line and highest point in the chest. Trocars are depicted by red circles. AP: accessory port



Figure 12. Left robotic selective sympathectomy. Intraoperative photograph depicts the robot in position. Three robotic arms are used

CONCLUSION

Significant controversies surround the minimally surgical treatment of hyperhidrosis. Historically, the interruption of the sympathetic chain has been associated with relief of hyperhidrosis but with high rates

of debilitating compensatory hyperhidrosis. Greater understanding of the anatomy and physiology of the sympathetic chain, and advances in minimally invasive surgical techniques and instruments have clarified many of the controversies. Selective division of the preganglionic and postganglionic sympathetic fibers from T2-T4 without interruption of the sympathetic chain has been associated with the greatest rate of anhidrosis and the lowest rates of compensatory hyperhidrosis. In more recent studies, there are indications that a bilateral staged approach may be preferable to bilateral simultaneous approach to selective dorsal sympathectomy for hyperhidrosis.

Although the results of bilateral staged robotic selective dorsal sympathectomy appear to be superior to that of previous procedures, many surgeons question the cost-effectiveness of the robotic procedure. The comparison of the hospital cost and clinical effectiveness of sympathectomy by video-assisted surgery (VATS) (thoracoscopic) or robotics has not been performed. However, a number of studies have studied the hospital cost and clinical effectiveness of robotic versus thoracoscopic and open lobectomy. Nishimura reviewed the literature for the cost of robotic lobectomy^[72]. Nine of the 18 published articles compared the cost of robotic lobectomy with VATS alone. All of these studies found a significantly higher total cost in the robotic group when compared to VATS. The intraoperative costs or charges were significantly higher in the robotic group. Interestingly, Kneuert *et al.*^[73] performed a propensity score-weighted comparison of the cost and perioperative outcomes of the three approaches to lobectomy for a 5-year period at a tertiary referral center^[73]. The propensity score comparison showed no statistical difference for the direct hospital cost between the three groups (robotic \$17,223, VATS \$17,260 and open \$18,075). In this study, postoperative complications and prolonged hospital stay added considerable hospital expenses. They concluded that the cost of robotic procedures needs to be placed in the context of the surgical outcomes. Specifically, in terms of the comparison of the cost of robotic versus VATS selective sympathectomy for hyperhidrosis, the increased cost of robotic instrumentation needs to be viewed within the perspective of the rate of anhidrosis and compensatory hyperhidrosis.

Finally, many experienced surgeons can perform a VATs sympathectomy in one hour or less, with two 5-mm ports and usually in the outpatient setting. Comparison of this approach to staged robotic selective staged sympathectomy needs to be viewed in the context of the rates of anhidrosis and perhaps most importantly the rate of compensatory hyperhidrosis, and viewed both from the perspective of the patient and that of the surgeon. Clearly the answer will be provided by a well-designed, prospective randomized approach which will compare the VATS to the robotic approach with very rigorous definition of anhidrosis and compensatory hyperhidrosis with inclusion of cost and quality of life considerations.

DECLARATIONS

Authors' contributions

Both authors contributed equally to the preparation of the manuscript.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Review

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Percutaneous mitral valve repair in patients with secondary mitral regurgitation and advanced heart failure

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Abstract

Advanced heart failure (HF) prevalence is increasing and ranges between 1% and 10% of the overall HF population, due to the growing number of patients with HF and their better treatment and survival in the last 20 years. The best treatment for these patients is represented by heart transplantation, which, unfortunately, is only available for a minority of them. A significant portion of patients with advanced HF has concomitant severe mitral regurgitation, which acts as a driving force in inducing and maintaining this end-stage condition in a vicious cycle. Percutaneous mitral valve repair with MitraClip is a treatment option to stop this vicious cycle, providing safer outcomes and clinical benefits in some of these patients. Preliminary clinical observations show a possible selective role for percutaneous mitral valve treatment with MitraClip as a bridge to transplantation, candidacy or recovery. Further evidence will be necessary to confirm these preliminary data and support this new treatment framework of patients with advanced HF.

Keywords: Mitral regurgitation, secondary mitral regurgitation, percutaneous mitral valve repair, advanced heart failure, heart transplantation, bridge therapy

INTRODUCTION

Mitral regurgitation (MR) is the most common valve disease worldwide, affecting at least 20% of patients aged > 65 years^[1]. Secondary MR (SMR) is the predominant and most clinically relevant form. Indeed, SMR, even when mild, correlates with higher adverse outcomes^[2]. While the ischemic vs. non-ischemic etiologies do not impact on these findings^[3], higher grades of SMR severity are associated with reduced



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Table 1. 2018 HFA-ESC criteria for defining advanced heart failure

Presence of all of the following criteria despite optimal guideline-directed treatment
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV]
2. Severe cardiac dysfunction (LVEF \leq 30%), isolated RV failure (e.g., ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and severe diastolic dysfunction or LV structural abnormalities according to HFpEF and HFmrEF ESC definitions
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing > 1 unplanned visit or hospitalization in the last 12 months
4. Severe impairment of exercise capacity of cardiac origin: 6 MWTD (< 300 m) or pVO ₂ (< 12-14 mL/kg/min)

ARVC: arrhythmogenic right ventricular cardiomyopathy; BNP: B-type natriuretic peptide; ESC: European Society of Cardiology; HFA: Heart Failure Association; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO₂: peak exercise oxygen consumption; RV: right ventricular; 6MWTD: 6-min walk test distance.

survival and progressive worsening of left ventricle (LV) dysfunction^[4,5]. Therefore, it is crucial to treat MR in a useful time window before these changes become irreversible^[5-7]. Among all the percutaneous treatment options for MR, MitraClip (Abbott, Illinois, USA) is the most adopted device with > 100,000 procedures performed worldwide. The first two randomized clinical trials on edge-to-edge transcatheter mitral valve repair (TMVR) vs. guideline-directed medical therapy (GDMT) in patients with heart failure (HF) and severe MR (COAPT^[8] and MITRA-FR^[9]) reported contrasting yet complimentary results. The resultant effect is a growing interest in finding those who can benefit the most from this procedure. On the contrary, little is known about those patients with advanced HF and poor prognosis treated with MitraClip implantation. Although this procedure may be considered futile in some of these cases, it can act as bridging therapy for further invasive treatments in others. The aim of this review is to analyze the impact of SMR and its percutaneous treatment in this unconventional setting.

ADVANCED HEART FAILURE

The clinical course of HF is characterized by gradual worsening of cardiac function and symptoms. This process may lead to a clinical phase where traditional treatments (e.g., GDMT, devices and surgery) are no longer effective, and advanced therapies [e.g., mechanical circulatory support (MCS) and heart transplantation (HTx)] or palliative care are needed. This clinical condition is called advanced HF. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles were previously used to classify these patients based on the presence of HF with reduced ejection fraction (HFrEF) and need for long-term MCS device implantation. To be more inclusive by extending this group also to patients affected by HF with preserved ejection fraction (HFpEF), an updated definition of the European Society of Cardiology has been released^[10] [Table 1].

Prevalence of advanced HF ranges between 1% and 10% of the overall HF population. This percentage is growing because of better treatment and longer survival of these patients. Once these patients have been identified, it is of utmost importance to acknowledge the appropriate timing for referring them to tertiary care centers where advanced therapies can be adopted. A useful mnemonic ("I Need Help") has been proposed to verify the eligibility to immediate management and transfer based on the need for inotropic therapy, end-organ dysfunction, poor ejection fraction, consistently low blood pressure and poor or intolerance to GDMT^[11] [Table 2].

Despite the efforts spent to categorize this stage of disease, we must recognize the extreme variability that exists between patients who are part of this group. In one extreme, there are young patients with idiopathic heart disease or non-ischemic cardiomyopathies (chemotherapy-induced, myocarditis-related, etc.) in the absence of further comorbidities. On the opposite side, we can find elderly people mainly affected by ischemic heart disease and numerous concomitant co-pathologies [chronic kidney disease (CKD), diabetes mellitus (DM), atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), peripheral vascular

Table 2. "I Need Help" - Markers of advanced heart failure

I	Inotropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	NYHA/Natriuretic peptide	Persisting NYHA class III/IV and/or persistently high BNP/NT-proBNP
E	End-organ dysfunction	Worsening renal or liver dysfunction in the setting of heart failure
E	Ejection fraction	Very low ejection fraction < 20%
D	Defibrillator shocks	Recurrent appropriate defibrillator shocks
H	Hospitalizations	More than 1 hospitalization with heart failure in the last 12 months
E	Edema/Escalating diuretics	Persisting fluid overload and/or increasing diuretic requirement
L	Low blood pressure	Consistently low BP with systolic < 90-100 mmHg
P	Prognostic medication	Inability to up-titrate (or need to decrease/cease) ACEI, beta-blockers, ARNIs, or MRAs

ACEI: angiotensin-converting enzyme inhibitor; ARNI: angiotensin-receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; BP: blood pressure; MRA: mineralocorticoid receptor antagonist; NT-ProBNP: N-terminal pro-b-type natriuretic peptide; NYHA: New York Heart Association

disease (PVD), *etc.*]. We must take this heterogeneity into consideration when examining the outcomes of the therapies adopted.

MANAGEMENT STRATEGIES IN ADVANCED HEART FAILURE

HTx remains the best option for most patients with advanced HF. The developments in recipient and donor selection, immunosuppression and management of infectious complications have led to considerable improvements in survival, exercise capacity, quality of life and return to work. However, the number of transplants seems to have reached a plateau in the last years, because of the limited availability of donor hearts. The marked imbalance between demand and supply results in continuous expansion of waiting lists and prolonged waiting times (over 12 months). Patients on "waiting list" are characterized by high mortality rate, ranging between 14% at 1 year and 20% at up to 3 years^[12]. HTx candidates in the current era are also more complex: older, antigen-sensitized and on MCS at the time of listing and transplantation. In this setting, our goal must be to allocate the limited resources available in the best possible way and, at the same time, achieve better outcomes.

Left ventricular assist device (LVAD) implantation is an established treatment for long-term MCS. First introduced for transplant-ineligible patients with advanced HF, its technology has been developed enough to make it a valid alternative as destination therapy. The Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) study demonstrated higher survival with improved functional status, improved quality of life and reduced depression in the LVAD group compared to OMT, at the expense of more hospitalizations and greater rate of major adverse events (e.g., bleedings, stroke, driveline infections, pump thrombi, ventricular arrhythmias and right HF)^[13].

Several percutaneous and paracorporeal devices are available for short term MCS. Their simple implantation and safety make them suitable for advanced HF patients until LVAD, HTx or candidacy to LVAD/HTx. For the latter purpose, the International Society for Heart Lung Transplantation suggests application of MCS in the case of potentially reversible or treatable comorbidities such as cancer, obesity, renal failure, tobacco use and pharmacologically irreversible pulmonary hypertension, with subsequent re-evaluation to establish candidacy (Class IIb; Level of Evidence: C)^[14]. Despite huge developments in technology, a significant portion of advanced HF patients decline MCS implantation for a variety of personal reasons or are not eligible for this therapy due to prohibitive operative risk, limited life expectancy, irreversible renal or hepatic dysfunction and severe psychosocial limitations. For these reasons, we have to consider the use of other devices, among which the MitraClip can play a leading role in case of advanced HF with concomitant severe MR.

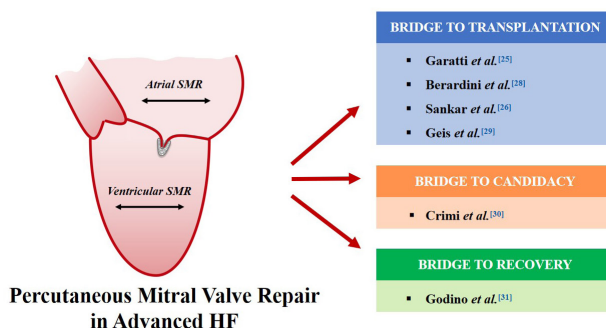


Figure 1. Published clinical evidence of MitraClip implantation in advanced HF patients with concomitant atrial or ventricular secondary mitral regurgitation pursuing the following strategies: bridge to heart transplantation, bridge to candidacy to heart transplantation and bridge to recovery. HF: heart failure; SMR: secondary mitral regurgitation

PROGNOSTIC ROLE OF MITRAL REGURGITATION ON ADVANCED HEART FAILURE

PATIENTS

A significant proportion of patients with advanced HF have concomitant MR: severe or moderate-severe MR is present in about 15% of them and moderate or worse MR in about 40%^[15]. Different etiological mechanisms underlie SMR. In HFpEF, SMR is mainly generated by an “atrial-secondary mechanism”: high left atrial pressure induces atrial and mitral annulus dilatation, with eventual atrial fibrillation [Figure 1]^[16]. In HFrEF, SMR is associated with a “ventricular-secondary” mechanism: dilatation and remodeling of LV cause mitral annulus dilation and papillary displacement tethering the valve leaflets and avoiding a competent coaptation [Figure 1]^[16]. This definition does not discern the two casual pathways of MR in the case of LV dysfunction: displacement and tenting of papillary muscles can be symmetrical as a consequence of marked LV dilatation (“true secondary” MR) or asymmetrical if caused by unequal or disordinated activation or contraction of the papillary muscles (e.g., left bundle branch block or inferior-posterior myocardial infarction).

From a purely pathophysiological point of view, it is important to understand that SMR can represent either a “primum movens” or an epiphenomenon of disease progression (“true secondary” MR), depending on the etiological mechanisms of MR and the clinical condition of patients [Figure 2]. It is not easy to discriminate in each patient the role of MR in the disease process. Recently, a conceptual framework that would allow physicians to distinguish between these two possibilities has been proposed^[17-19].

According to this concept, we can estimate the contribution of global LV function to the severity of MR by measuring the LV end-diastolic volume (LVEDV). When MR is completely secondary (“true secondary” MR) and it is just a biomarker of LV dysfunction and remodeling, the magnitude of MR flow would be “proportionate” to and thus explicable by the LVEDV. Conversely, if MR is the “primum movens” (primary cause of the disease), the magnitude of MR would be “disproportionate” and greatly exceed that predicted by LV volumes. The ratio between effective regurgitant orifice area (EROA) and LVEDV is helpful in defining the degree of MR as proportionate ($EROA/LVEDV \leq 0.14$) or disproportionate ($EROA/LVEDV > 0.14$) with the extent of LV dysfunction^[17,20].

Consequently, the response to therapeutic intervention (TMVR on top of GDMT) will be more relevant in patients in which MR is the “primum movens” of the disease and less beneficial when MR is the consequence of LV dilatation and remodeling. The validity of this theory was tested by analyzing the outcome after MitraClip procedure of MITRA-FR and COAPT populations^[17]. Accordingly, we can try to identify four cohorts of patients with specific clinical phenotypes and different goals which can be achieved with TMVR:

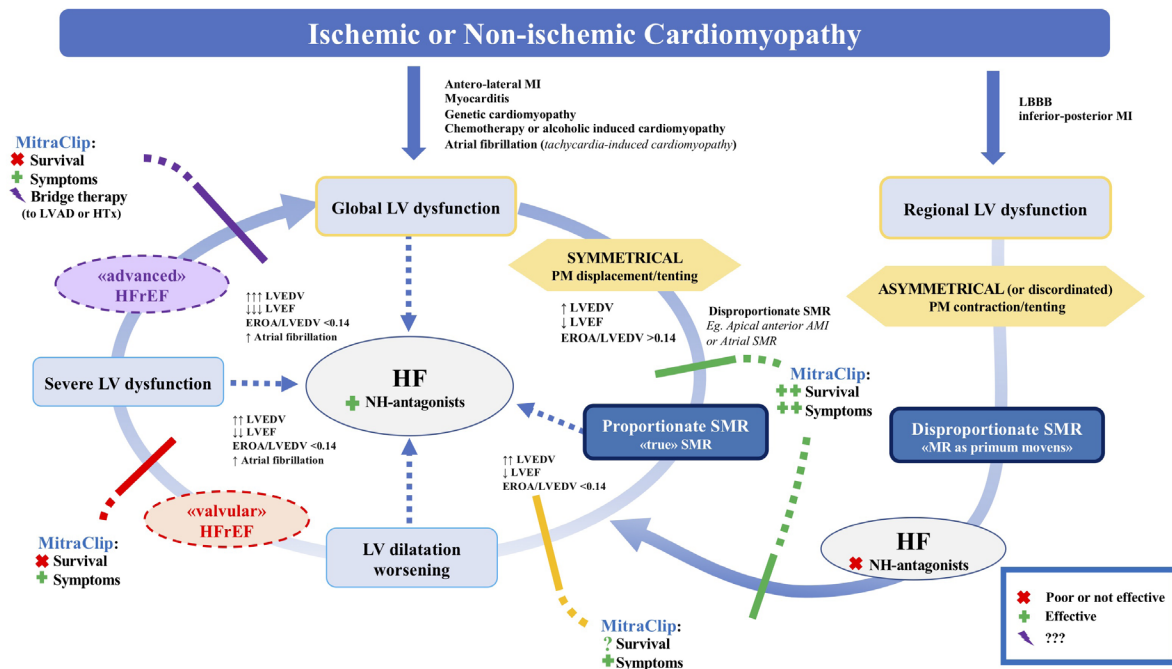


Figure 2. Prognostic role of secondary mitral regurgitation and impact of transcatheter mitral valve repair. The impact of transcatheter mitral valve repair on four cohorts of patients with specific clinical phenotypes: (1) The green line indicates patients with disproportionate MR (MR is the “primum movens”) exhibiting both symptoms and mortality reduction (5 COAPT subgroups, 492 patients), including patients with disproportionate MR, symmetrical LV dysfunction, and PM displacement/tenting (e.g., apical anterior AMI); (2) The yellow line indicates patients with proportionate MR reporting unclear prognostic benefit (COAPT subgroup, 56 patients); (3) The red line indicates patients with proportionate MR exhibiting only symptoms reduction (MITRA-FR patients, 304 patients); (4) The purple line indicates advanced HF patients with proportionate MR showing clinical and hemodynamic stabilization (or improvement) as bridge therapy. AMI: acute myocardial infarction; HF: heart failure; HFREF: heart failure with reduced ejection fraction; HTx: heart transplantation; LBBB: left bundle branch block; LV: left ventricle; LVAD: left ventricular assist device; LVEDV: left ventricle end diastolic volume; LVEF: left ventricle ejection fraction; MI: myocardial infarction; NH: neurohormonal antagonist (beta-blockers, ACE-inhibitors, RAAS blockers, Nephilysin, *etc.*); PM: papillary muscle; SMR: secondary mitral regurgitation. Adapted and modified from Godino *et al.*^[7]

1. Patients with disproportionate MR (in which MR is the “primum movens”) exhibiting both symptoms and mortality reduction (COAPT subgroups, 492 patients); patients with disproportionate MR caused by PM displacement/tenting in a symmetrical LV dysfunction (e.g., apical-anterior acute myocardial infarction); and patients with HFpEF and/or AF causing *disproportionate* MR due to mitral annulus dilatation (atrial-secondary MR) (the green line in [Figure 2](#)).
2. Patients with proportionate MR (“true secondary” MR) exhibiting only symptoms reduction (304 MITRA-FR patients) (the red line in [Figure 2](#)).
3. Patients with proportionate MR reporting unclear prognostic benefit (COAPT subgroup, 56 patients) with “MITRA-FR like” survival at 1 year and “COAPT-like” survival at 2 years (the yellow line in [Figure 2](#))^[21]

The latter group is underrepresented but suggests that a significant benefit cannot be excluded also for patients with “true secondary MR” treated in an early phase of the HF process, before progression to severe LV dilation and before AF onset. All these considerations should be appraised as preliminary and, in any case, not absolute, because they are derived from the post hoc analysis of the COAPT trial and based on relatively small numbers of patients. This theory was tested in a “real-world” population; however, the absence of significant differences may have been undermined by the presence of few patients with proportionate MR (according to Grayburn’s cut-off)^[22]. Therefore, this conceptual framework of proportionate/disproportionate MR needs to be weighed and confirmed on larger patient series before being considered as a definitive risk-benefit threshold^[17].

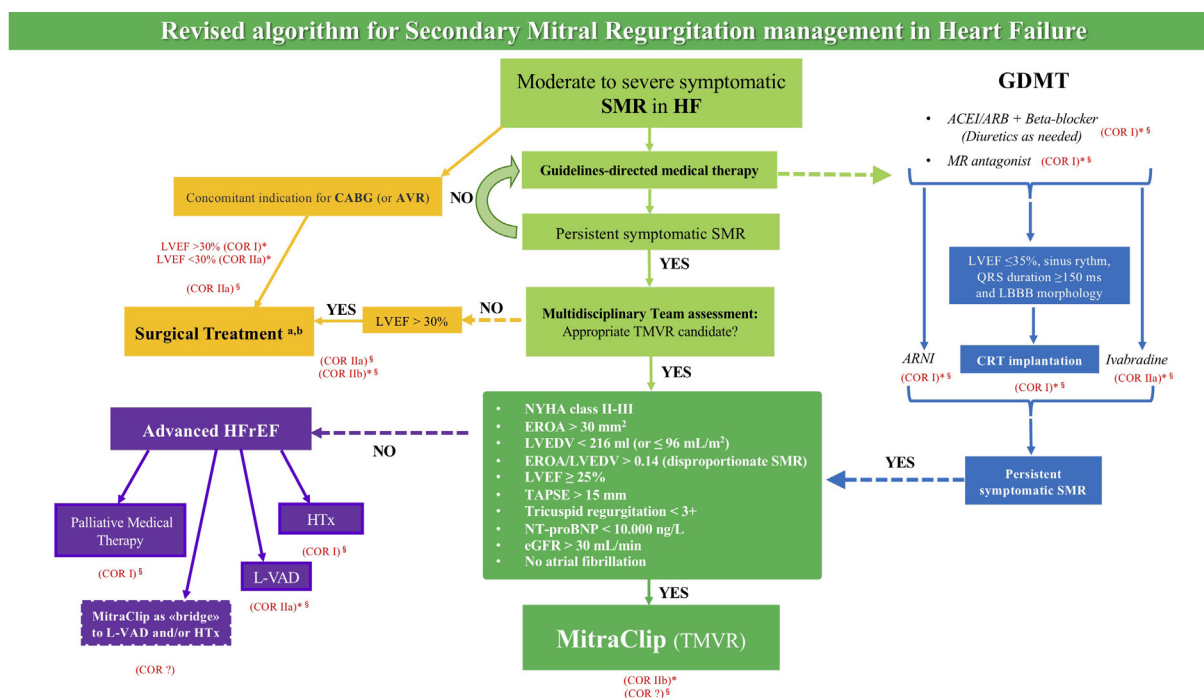


Figure 3. Revised algorithm for secondary mitral regurgitation management in heart failure. Symptomatic, NYHA Class II-IV. Evaluation of clinical context, symptomatology, etiology of MR, and MR severity using a multiparametric approach. *ESC/EACTS/HFA Guidelines; SACCC/AHA/HFSA Guidelines. a: in patients undergoing CABG or AVR, ACC/AHA/HFSA Guidelines do not consider baseline LVEF in the therapeutic decision-making process for concomitant valvular surgery; b: according to ACC/AHA/HFSA Guidelines, it is reasonable to choose chordal-sparing mitral valve replacement for chronic severe ischemic SMR (COR IIa), whereas mitral valve repair or replacement may be considered for chronic severe secondary MR (COR IIb) in patients undergoing isolated mitral surgery. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; AVR: aortic valve replacement; CABG: coronary artery by-pass graft; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; COR: class of recommendation; CRT: cardiac resynchronization therapy; eGFR: estimated glomerular filtration rate; EROA: effective regurgitant orifice area; GDMT: guideline-directed medical therapy; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HTx: heart transplantation; LBBB: left bundle branch block; Log EuroSCORE: Logistic European System for Cardiac Operative Risk Evaluation; L-VAD: left ventricular assist device; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MR: mineralocorticoid receptor; NT-proBNP: N-terminal pro-B type natriuretic peptide; NYHA: New York Heart Association; SMR: secondary mitral regurgitation; TAPSE: tricuspid annular plane systolic excursion. Adapted and modified from Godino *et al.*^[7]

Despite these limitations, we can reasonably assume that most of patients with advanced HF exhibit the classic pathophysiologic features of “true secondary” MR (proportionate MR) together with other unfavorable co-pathologies (CKD, DM, AF, PVD and severe COPD). In these cases, a less favorable response is to be expected after TMVR with MitraClip, because the underlying advanced cardiomyopathy and the co-pathologies are not the direct target of the intervention. However, even the mere symptoms reduction and the hemodynamic stabilization can be important goals for most of these patients and can be achieved with the combination of GDMT and TMVR:

- Advanced HF patients with proportionate MR aim for clinical and hemodynamic stabilization (or improvement) as bridge therapy (the purple line in [Figure 2](#)).

To combine the current guideline recommendations based on available evidence together with the recently published frameworks for MR and the unexplored setting of advanced HF, we propose a revised algorithm for SMR management in HF patients [Figure 3]^[7,23].

MITRACLIP THERAPY IN ADVANCED HF PATIENTS

The aforementioned analysis of MITRA-FR and COAPT patients in conjunction with further investigations will guide us towards the identification of who will benefit the most from TMVR and which is the proper

timing of intervention. On the contrary, limited data are available regarding advanced HF patients who are excluded from randomized clinical trials and for which the only available evidence derives from observational studies.

Clinical evidence

We can identify the following strategies in performing percutaneous mitral valve repair in advanced HF patients [Figure 1]:

1. Bridge to heart transplantation (BTT)
2. Bridge to HTx candidacy (BTC)
3. Bridge to recovery (BTR)

One of the first papers on MitraClip procedure, reported by Franzen *et al.*^[24] in 2011, showed for the first time that MitraClip implantation was safe and significantly improved the New York Heart Association (NYHA) class of patients with end-stage/advanced HF, especially of those who had significant reduction of MR grade after the procedure. In 2015, Garatti and colleagues described a case report in which the percutaneous mitral valve repair was effective as a BTT^[25]. Similarly, Sankar *et al.*^[26] implanted a MitraClip and a Carillon device (Cardiac Dimensions, Kirkland, WA, USA) in the same patient with the aim of BTT, replicating the surgical counterpart known as “Alfieri technique”^[27]. In a larger cohort of 75 advanced HF patients, the following were observed: symptoms improvement, re-hospitalizations reduction and lower pro-BNP levels after percutaneous mitral valve repair with MitraClip, despite the lack of LV reverse remodeling^[28].

Further evidence derives from a German^[29] proof of concept case series showing that MitraClip is not only feasible in advanced HF patients listed for HTx, but also leads to favorable hemodynamic effects such as lower pulmonary artery pressures. Similar results were described by an Italian^[30] group in which the reduction of pulmonary vascular resistances led to the absence of further hospital admissions for HF and reclassification of these patients who became eligible for HTx. The goal in the latter study was to make use of the percutaneous device as BTC. Another report published in 2017 proved that the MitraClip can promote such a benefit as leading to HTx delisting following an optimal clinical and echocardiographic recovery^[31]: an initial BTT strategy turned into a BTR.

MitraBridge study registry

The ongoing “MitraBridge” registry, presented at EuroPCR 2019, was conducted with the aim of better understanding the outcome after MitraClip in this extreme setting of patients^[32]. This international, multicenter registry collected data for nearly 100 end-stage HF patients treated with the percutaneous device as bridge strategy. Baseline characteristics were clearly different from those belonging to MITRA-FR and COAPT populations: despite a younger age [57.5 years (50-63), median and interquartile range], there were reported lower values of mean ejection fraction (27%), higher percentage of NYHA Classes III-IV (96%), higher mean left ventricular end diastolic volumes indexed (134 mL/m²), elevated mean systolic pulmonary artery pressures (sPAP, 51 mmHg) and mean pulmonary capillary wedge pressures (25 mmHg) and the majority (43%) had an INTERMACS profile of 5-6. At 1 year, two thirds of the cases achieved a primary composite endpoint of elective HTx, entering (or remaining) in HTx list and delisting for clinical improvement; the rest of the patients who did not reach those events were death, implanted with LVAD, transplanted urgently or still waiting for HTx listing. The patients who were delisted exhibited significant clinical improvement represented by marked reductions in NYHA class, sPAP and MR grade, which allowed a BTR.

At present, there is still little knowledge about the real effectiveness and applicability of the MitraClip procedure in the case of advanced HF. Although this procedure is almost ineffective for some of the patients

with advanced HF, it can act as a “bridge” for further invasive treatments (e.g., HTx or MCS) for others. It must be clear that the final goal to perform such interventions in this setting of patients is no longer reducing mortality of course, but to enhance and/or stabilize the clinical status (mainly by reductions of sPAP) and thus the quality of life while awaiting HTx. Consequently, obtaining a symptomatic benefit increases the chances of reaching HTx in a good enough clinical status. More research efforts need to be spent to understand who will more likely benefit from percutaneous mitral valve repair at this stage of the HF. Currently, it is recommended to early refer patients affected by advanced HF to tertiary care centers that can best individualize treatment options (HTx, MCS and bridging solutions) and assure the proper timing for their application.

CONCLUSION

MitraClip implantation in advanced HF patients with concomitant severe MR is safe and can provide significant clinical improvement. Available evidence describes the favorable outcomes obtained with this device resulting in BTT, BTC or BTR. Further studies are needed to investigate the predictors of success for this procedure in this extreme setting of patients in order to provide solid basis for treatment recommendations.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Scotti A, Godino C

Provided final revision and administrative support: Margonato A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Technical Note

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Advances and understanding pitfalls of laparoscopic transhiatal esophagectomy with *en bloc* mediastinal lymph node dissection

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Abstract

We began performing mediastinal lymph node dissection using the laparoscopic transhiatal approach in 2009. Following the initiation of the single-port mediastinoscopic cervical approach in 2014, we developed a technique for transmediastinal radical esophagectomy without a thoracic approach. We herein describe our surgical procedures for *en bloc* mediastinal lymph node dissection by the laparoscopic transhiatal approach with a focus on pitfalls. We opened the esophageal hiatus and the working space was secured using long retractors. During division of the right crus of the diaphragm, we made efforts to avoid damaging the left hepatic vein and inferior vena cava. Dissection of the posterior plane of the pericardium was extended to the cranial side, and the bilateral inferior pulmonary veins were identified. To avoid misorientation, the posterior plane was initially extended along the long axis of the esophagus. The anterior and posterior sides of the posterior mediastinal lymph nodes were then both dissected. These lymph nodes were lifted in a sheet-like form and then cut along the borderline of the left mediastinal pleura. The right side of the mediastinal lymph nodes was then dissected. To avoid damaging the arch of the azygos vein, it was identified at the dorsal side of the right main bronchus prior to lymph node dissection. This procedure decreased the total operative time, total operative bleeding, and postoperative respiratory complications without reducing the quality of lymphadenectomy. In conclusion, the procedure described herein resulted in a good surgical view and safe *en bloc* mediastinal lymph node dissection. A detailed understanding of mediastinal 3D anatomy and specific pitfalls is crucial for the successful use of this approach.



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Keywords: Transmediastinal radical esophagectomy, laparoscopic transhiatal approach, pitfall

INTRODUCTION

Transthoracic esophagectomy with mediastinal lymphadenectomy has been the standard procedure for esophageal squamous cell carcinoma^[1,2]. However, esophagectomy via right thoracotomy is highly invasive, and respiratory morbidity is still one of the most common complications^[3]. Since Orringer and Sloan^[4] reported the clinical application of transhiatal esophagectomy, it has been broadly performed because it prevents respiratory complications. Although laparoscopic transhiatal esophagectomy, initially described by DePaula *et al.*^[5], has also been performed^[5-7], a technique for mediastinal lymphadenectomy had not yet been established because of the limited surgical view and difficulties associated with surgical procedures.

We began performing esophagectomy using the laparoscopic transhiatal approach for esophageal cancer in 2009 to reduce the duration of one-lung ventilation, and, to date, more than 400 patients have undergone our method during various esophageal surgical procedures^[8-11]. We noted the advantages of this approach, and developed a novel technique for lower mediastinal lymph node dissection^[8,10]. By applying the same concept to middle mediastinum, we developed a new procedure for subcarinal lymph node dissection using the laparoscopic transhiatal approach^[12,13]. We also started using the single-port mediastinoscopic cervical approach in 2014, and developed a simple technique for transmediastinal radical esophagectomy without a thoracic approach (more than 200 patients)^[14-17].

We herein describe our surgical procedures for *en bloc* resection of the middle and lower mediastinal lymph nodes by the laparoscopic transhiatal approach, with a focus on pitfalls for safe surgery.

SURGICAL PROCEDURES AND PITFALLS

Position, port placement, and devices

Patients were placed in the supine position, and we initially performed cervical and upper mediastinal lymphadenectomy using the left cervical single port technique^[14-16]. We recently performed middle mediastinal lymph node dissection via the cervical approach. Abdominal surgery was conducted using hand-assisted laparoscopic surgery (HALS), followed by lower mediastinal surgeries using the laparoscopic transhiatal approach. In cases in which middle mediastinal lymph node dissection was difficult to perform via the cervical approach, the laparoscopic transhiatal approach was employed.

We made an incision (70 mm) in the upper abdomen and inserted a lap disc (regular) (Ethicon, Cincinnati, OH, USA)^[11]. We introduced three 12-mm ports (right side of the umbilicus, left hypochondrium, and left flank), and one 5-mm port (left side of the umbilicus) for a flexible laparoscope^[11]. The surgeon stayed at the patient's right side, and the 12-mm port in the right side of the umbilicus was chiefly used for surgery. The assistant stayed on the left side, and two long retractors were inserted and used from ports in the left abdomen (UMIHIRA Co., Ltd., Japan). The scopist remained at the patient's groin [Figure 1]^[11].

Approach to the esophageal hiatus

Carbon dioxide was introduced into the abdominal space, and pneumoperitoneal pressure was held at 10 mmHg^[8-12]. We opened the esophageal hiatus, and carbon dioxide was introduced into the mediastinum. The use of long sealing devices is important for the laparoscopic transhiatal approach. The surgical view in the mediastinum was maintained by the surgeon's left hand, two long retractors, and pneumomediastinal pressure^[11]. The bilateral mediastinal pleura were preserved as much as possible because pneumomediastinal pressure is essential for securing a narrow mediastinal surgical space.

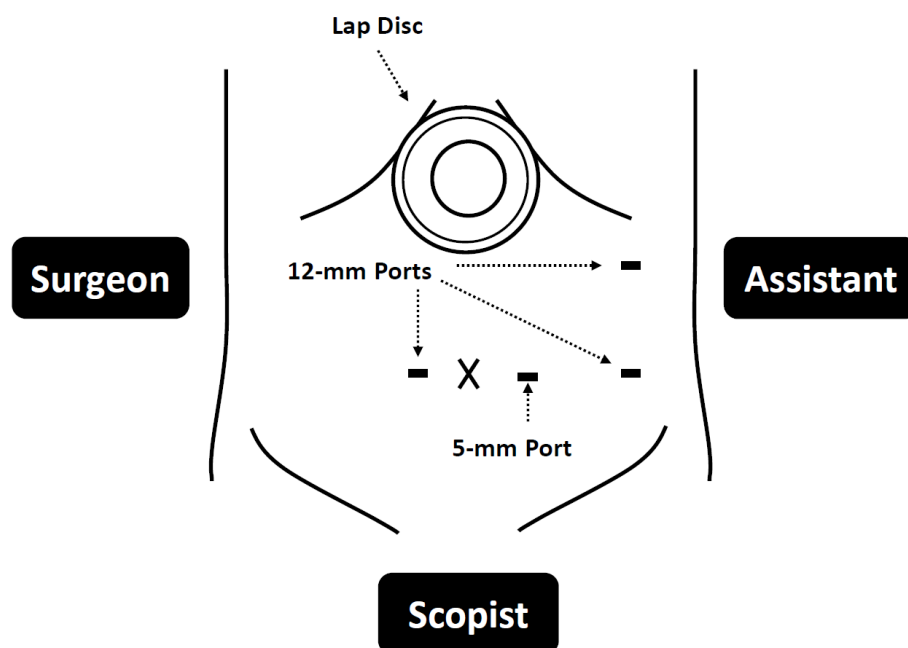


Figure 1. Intraoperative view of ports and incision locations on the abdomen^[11]. A lap disc was inserted into the upper abdomen. Three 12-mm ports were introduced (right side of the umbilicus, left hypochondrium, and left flank), and one 5-mm port for a flexible laparoscope was inserted into the left side of the umbilicus

Pitfall

Operability by the HALS technique was very good at the left side of the esophageal hiatus, but was poor at the right side. Therefore, to obtain a sufficient surgical view of the right inferior mediastinal space, we divided the right crus of the diaphragm [Figure 2A]. Following its division, the esophagus was moved to the dorsal side. In this step, we made every effort to avoid damaging major vessels, such as the left hepatic vein and inferior vena cava, which are located near the right crus of the diaphragm [Figure 2B]. A detailed understanding of 3D images of these major vessels preoperatively is important.

Exposure of the pericardium and inferior pulmonary vein

In the inferior mediastinal space, we divided pericardial adipose tissue and exposed the pericardium. Dissection of the posterior plane of the pericardium was extended to the cranial side, and the bilateral inferior pulmonary veins were identified. This plane was extended to the left side of the esophagus, and abruption of the anterior sides of the posterior mediastinal lymph nodes was conducted^[8-12].

Pitfall

In this step, a detailed understanding of 3D images of the left inferior pulmonary vein is crucial. The pericardium was initially exposed, and this surgical plane was extended. Since the extension of this surgical plane to the left side in advance may separate the ventral side of the inferior pulmonary vein [Figure 3A and B], it was important to initially extend the plane along the long axis of the esophagus [Figure 3C and D]. By extending the plane bilateral side, the dorsal side of the inferior pulmonary vein was clearly identified [Figure 3C and D].

Subcarinal and main bronchus lymph node dissection

In cases that underwent subcarinal lymph node dissection using the laparoscopic transhiatal approach, dissection of the posterior plane of the pericardium was extended to the level of the carina using a long sealing device, and the anterior side of the subcarinal lymph nodes and those of the bilateral main bronchi were dissected.

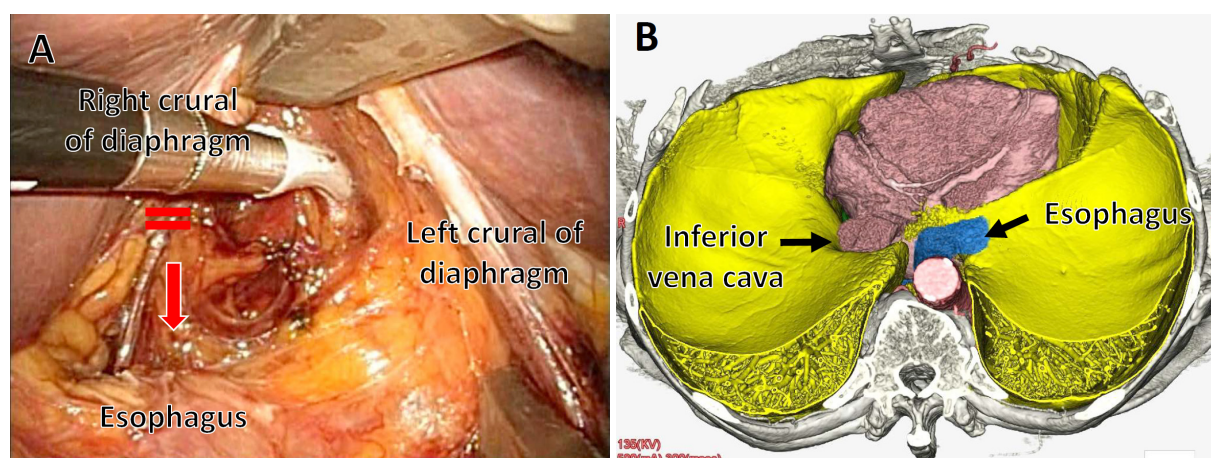


Figure 2. Pitfall around the right crus of the diaphragm. After cutting the right crus of the diaphragm (red double line), the esophagus was moved to the dorsal side (red arrow), and a sufficient surgical view of the inferior mediastinal space was obtained (A); at this point, major vessels, such as the inferior vena cava, were located near to the right crus of the diaphragm (B)

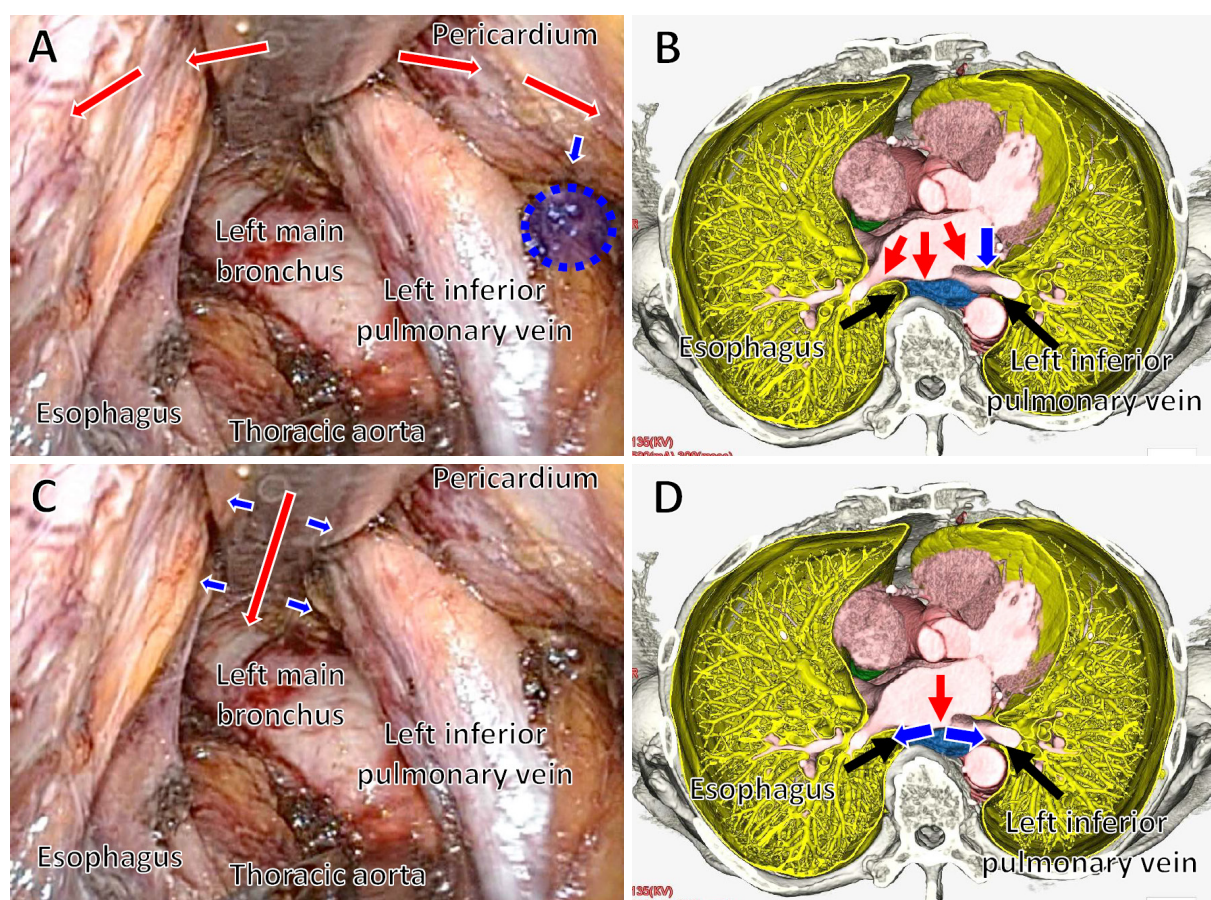


Figure 3. Pitfall around the left inferior pulmonary vein. The pericardium was initially exposed, and the surgical plane was extended. The extension of this plane to the bilateral side in advance (red arrows and circle) (A, B); to avoid misorientation, it was important to initially extend the plane along the long axis of esophagus (red arrows) (C, D). By extending the plane to the bilateral side (blue arrows), the dorsal side of the inferior pulmonary vein was certainly identified

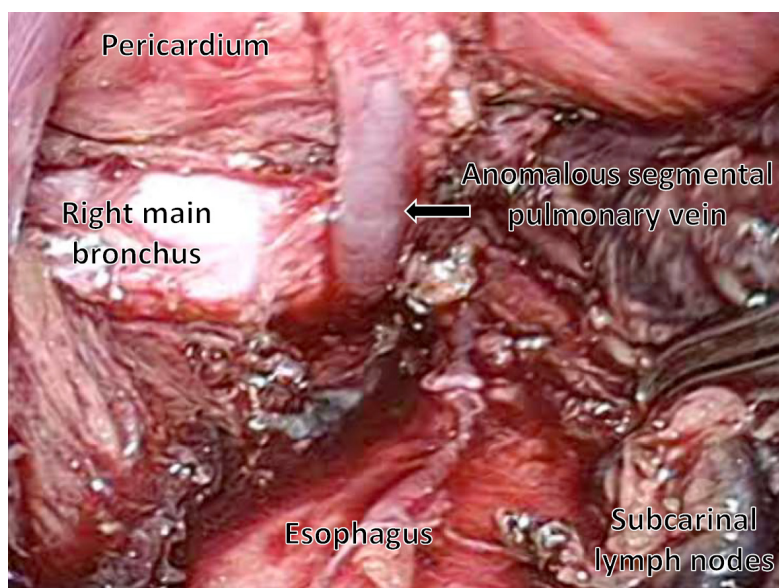


Figure 4. Anomalous pulmonary vein. An aberrant segmental vein in the right upper lobe that independently drained into the left atrium was identified (arrow). This anomalous vein penetrated the subcarinal lymph nodes and crossed behind the right main bronchus

Pitfall

In subcarinal dissection using the laparoscopic transhiatal approach, we need to consider anomalies of the pulmonary vein^[18]. We encountered and reported the rare abnormality of an aberrant segmental vein in the right upper lobe that independently drained into the left atrium^[18]. This anomalous vein penetrated the subcarinal lymph nodes and crossed behind the right main bronchus [Figure 4]. Although the anomalous pulmonary vein in the present case was not diagnosed preoperatively, our surgical procedure enabled the intraoperative identification of this vein and safe *en bloc* subcarinal dissection^[18].

Abruption of the ventral side of the thoracic aorta

We exposed the adventitia of the thoracic aorta at the level of the crural diaphragm, and dissected the anterior side of the thoracic aorta to the cranial side. The roots of the proper esophageal arteries were identified [Figure 5A] and divided using the long sealing device^[8-12].

Pitfall

When the proper esophageal arteries were divided using the sealing device, the assistant needed to decrease tension by the long retractor in order to avoid arterial damage [Figure 5B].

Dissection of the left side of posterior mediastinal lymph nodes

After these procedures, the anterior and posterior sides of the posterior mediastinal lymph nodes, including the thoracic para-aortic and left pulmonary ligament lymph nodes, were both dissected. These lymph nodes were lifted in a sheet-like form and cut along the borderline of the left mediastinal pleura, and, thus, the posterior mediastinal lymph nodes were dissected *en bloc*^[8-12] [Figure 6]. In cases that underwent middle mediastinal lymph node dissection using the laparoscopic transhiatal approach, this incision was extended to the left pulmonary hilum and the lymph nodes were dissected from the left main bronchus.

Dissection of the right side of mediastinal lymph nodes

In the dissection of the right side, an incision was made while lifting the right mediastinal pleura in a sheet-like form. In cases that underwent middle mediastinal lymph node dissection using the laparoscopic transhiatal approach, the incision was extended to the right pulmonary hilum, and the lymph nodes were

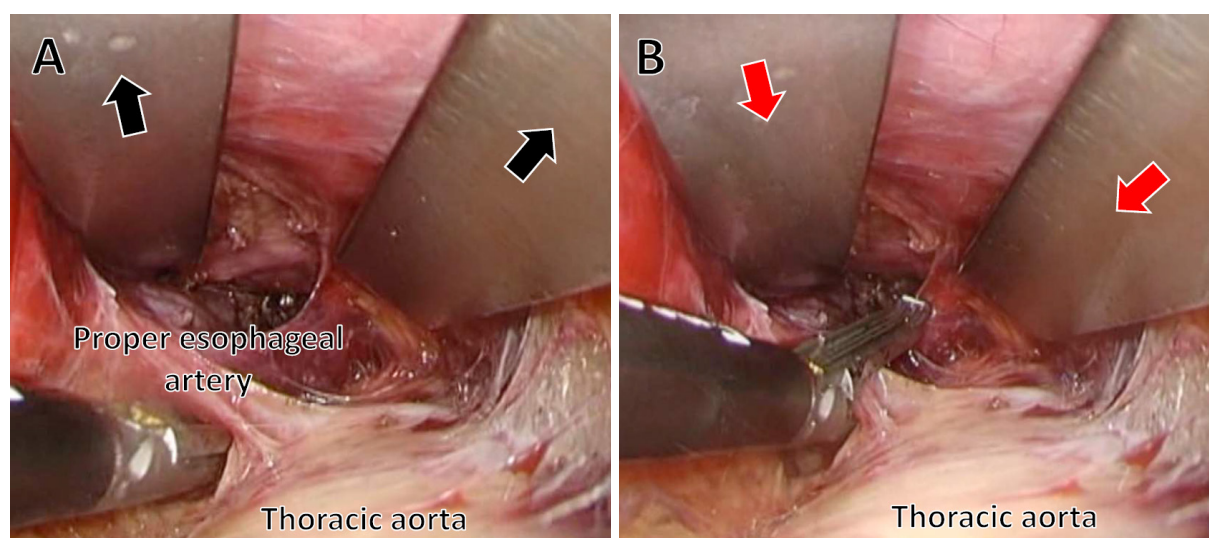


Figure 5. Pitfall around proper esophageal arteries. The adventitia of the thoracic aorta was exposed, and dissection of the anterior side of the thoracic aorta to the cranial side was performed. The roots of the proper esophageal arteries were identified. Black arrows showed the direction of tension given by the long retractor (A); when the proper esophageal arteries were divided using the sealing device, the assistant needed to decrease tension by the long retractor (red arrows) to avoid arterial damage (B)

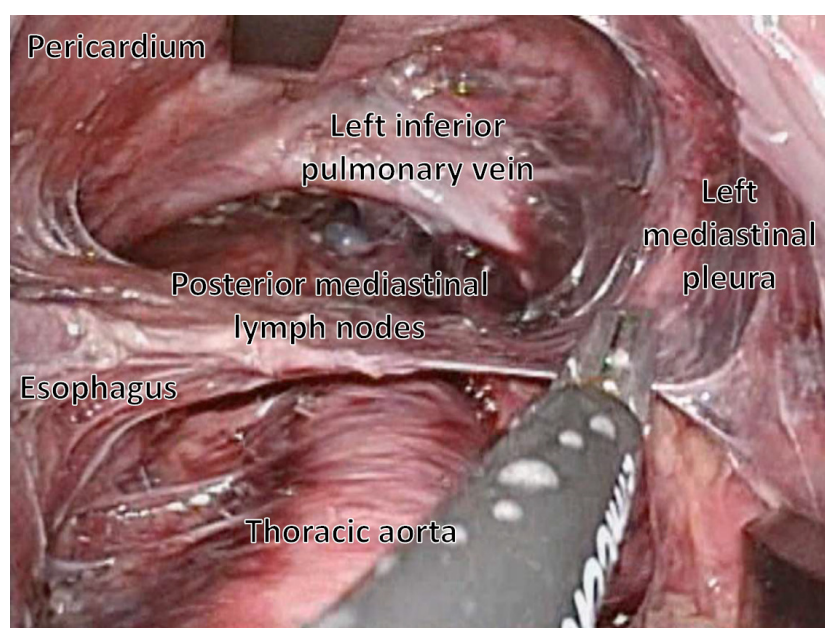


Figure 6. *En bloc* dissection of posterior mediastinal lymph nodes. The anterior and posterior sides of the posterior mediastinal lymph nodes were both dissected. These lymph nodes were lifted in a sheet-like form and cut along the borderline of the left mediastinal pleura

separated from the right main bronchus and tracheal bifurcation. The middle and lower mediastinal lymph nodes were dissected *en bloc*.

Pitfall

In this step, a detailed understanding of 3D images of the azygos vein is essential. At the lower mediastinal level, the azygos vein is located on the left side [Figure 7A]. However, at the middle mediastinal level, its position gradually changes to the right side [Figure 7B]. It then flows into the superior vena cava at the

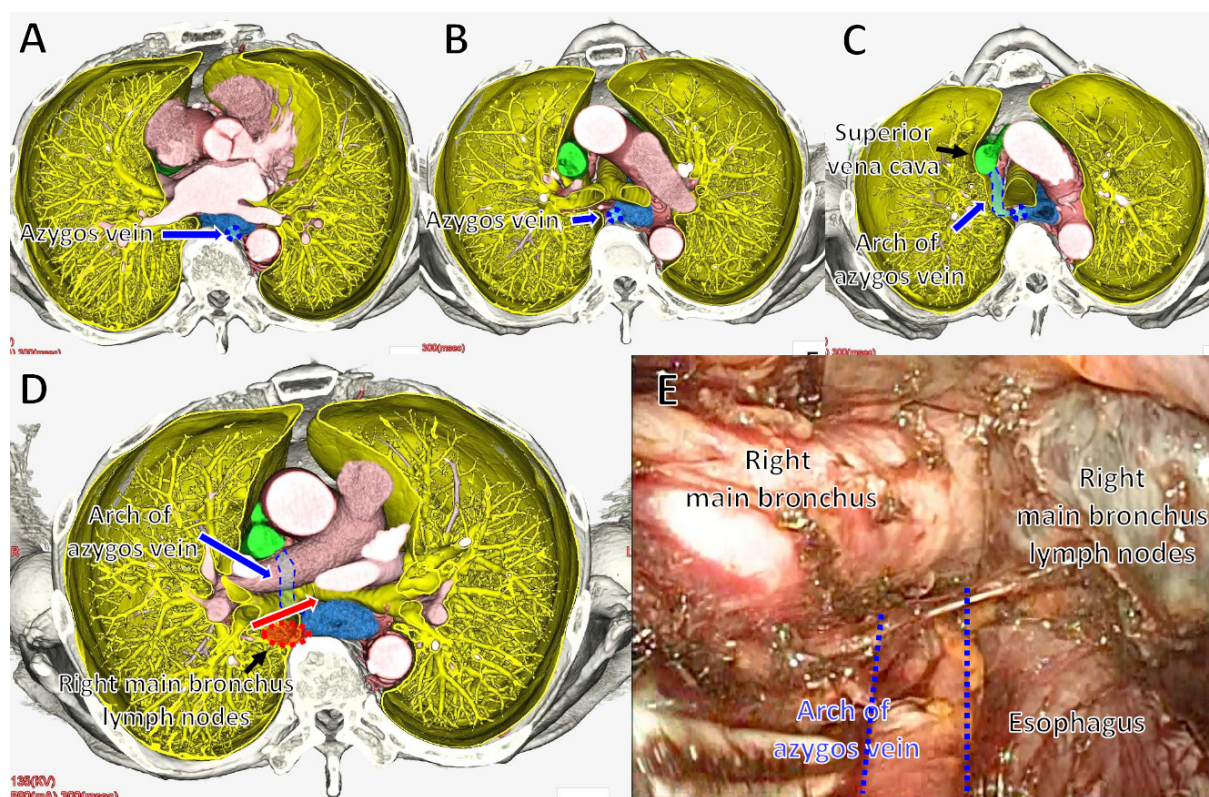


Figure 7. Pitfall around the azygos vein. At the lower mediastinal level, the azygos vein (blue arrow) is located on the left side (A); at the middle mediastinal level, the position of the azygos vein (blue arrow) gradually changes to the right side (B); the arch of the azygos vein (blue arrow) flows into the superior vena cava at the cranial side of the right main bronchus (C); in right main bronchus lymph node (red circle) dissection, these lymph nodes are resected from the right main bronchus (red arrow). At this point, there is the risk of damage to the arch of the azygos vein (blue arrow) (D); to avoid damage, it is important to identify the arch of the azygos vein (blue dotted lines) at the dorsal side of the right main bronchus prior to right main bronchus lymph node dissection (E)

cranial side of the right main bronchus [Figure 7C]. In our procedure for right main bronchus lymph node dissection, after the ventral and caudal sides were separated, these lymph nodes were resected from the right main bronchus. At this point, there was a risk of damage to the arch of the azygos vein [Figure 7D]. To avoid this, it was important to identify the arch of the azygos vein at the dorsal side of the right main bronchus prior to right main bronchus lymph node dissection [Figure 7E]. We also avoided damaging the membranous portion of the right main bronchus at this point.

DISCUSSION

Recent advances in the development of surgical devices and the standardization of operative procedures have resolved the conventional limitations associated with transmediastinal esophagectomy, such as difficulties maintaining a surgical field and operability. We previously reported the significance of transmediastinal radical esophagectomy as a minimally invasive surgery^[10-13,16]. This procedure initially reduced the incidence of postoperative respiratory complications because neither thoracotomy nor two-lung ventilation is performed. The total operative time may have been decreased because a change in position during surgery was not necessary in this approach. We previously compared the treatment outcomes of 84 patients with esophageal cancer who underwent mediastinal lymph node dissection by the laparoscopic transhiatal approach with those of 75 patients who underwent dissection by right thoracotomy^[11]. The total operative time was significantly shorter in patients treated with the laparoscopic transhiatal approach (332.4 ± 106.2 min) than in those treated with right thoracotomy (435.7 ± 98.0 min)^[11]. Furthermore, a magnified view of the deep mediastinal space using a mediastinoscope decreased the total

operative bleeding and improved the quality of lymphadenectomy. We also found that total operative bleeding was significantly less in patients treated with the laparoscopic transhiatal approach (216.2 ± 193.1 mL) than in those treated with right thoracotomy (549.5 ± 390.4 mL), and that the total number of resected lymph nodes did not significantly differ between the two groups (laparoscopic transhiatal approach: 35.9 ± 16.0 /right thoracotomy: 40.1 ± 20.3)^[11].

On the other hand, a detailed understanding of mediastinoscopic esophagectomy is essential for the success of this procedure. The narrow mediastinal surgical space needs to be secured by appropriate retraction and pneumomediastinal pressure in this method. In addition, we sequentially expose the mediastinal organs using a long surgical device, and, thus, this surgery is similar to “tunnel construction”. A detailed understanding of the 3D anatomy of the mediastinum is important. We routinely construct 3D images from CT scans and attempt to recognize the specific anatomy of major vessels preoperatively. A detailed understanding of pitfalls is indispensable to ensure safety, and the development of procedures to overcome the pitfalls of this approach, such as the tangential view, is needed.

Robot-assisted transmediastinal radical esophagectomy was recently reported to achieve a better quality of life than open esophagectomy in both retrospective and prospective studies^[19-22]. Larger studies and prospective analyses are needed for comparisons between robotic and laparoscopic transhiatal approaches. In the future, the development of novel instruments, such as small-caliber devices with multiple joints, and lightweight robotic single-port techniques may be key innovations in transmediastinal radical esophagectomy.

CONCLUSION

Laparoscopic transhiatal esophagectomy provided a good surgical view and safe *en bloc* mediastinal lymph node dissection in patients with esophageal cancer. The standardization of surgical procedures and a detailed understanding of the mediastinal 3D anatomy and specific pitfalls are important for the success of this approach.

DECLARATIONS

Authors' contributions

Wrote the manuscript: Shiozaki A, Fujiwara H, Otsuji E

Performed surgeries: Shiozaki A, Fujiwara H, Konishi H

Designed the research: Shiozaki A, Fujiwara H, Konishi H, Shimizu H, Kudou M, Arita T, Kosuga T, Morimura R, Kuriu Y, Ikoma H, Kubota T, Okamoto K, Otsuji E

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Our work conforms to the guidelines set forth in the Helsinki Declaration concerning human and animal rights, and we followed the policy concerning informed consent. The study of this surgical procedure was reviewed and approved by the Kyoto Prefectural University of Medicine Institutional Review Board.

Consent for publication

Written informed consent for publication was obtained.

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Review

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Robotic esophagectomy: how I do it?

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Abstract

Compared to the open approach, minimally invasive esophagectomy (MIE) offers several advantages including smaller incisions with decreased pain, improved cosmesis, and earlier return of the patient to baseline function. Robotic-assisted minimally invasive esophagectomy (RAMIE) builds on standard MIE by offering three-dimensional visualization, better instrument articulation, tremor filtration, and superior ergonomics, all of which facilitate technical precision and surgeon comfort. An evolving literature demonstrates that when performed by experienced surgeons, RAMIE leads to improved perioperative outcomes with long-term oncologic equivalency to open approaches, and may offer advantages compared to traditional MIE. This review focuses on the key steps of performing 3-field McKeown, 2-field Ivor Lewis, and transhiatal robotic esophagectomies, data regarding the short- and long-term outcomes, and a brief overview of upcoming trials comparing RAMIE with MIE.

Keywords: Esophagectomy, robotic, minimally invasive esophagectomy

INTRODUCTION

Over the last two decades or more, minimally invasive approaches to esophagectomy have been adopted with increasing frequency. The benefits of minimally invasive surgery include smaller incisions, less pain, improved cosmesis, decreased lengths of stay, and quicker return of the patient to baseline function. When performed for thoracic malignancies, minimally invasive resections have led to cure rates equivalent to



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those found from open procedures^[1-5]. These results have translated more recently to robotic surgery as well. The first minimally invasive esophagectomy (MIE) was reported in 1992^[6], and the first robotic-assisted minimally invasive esophagectomy (RAMIE) with an intrathoracic anastomosis was published in 2002^[7]. This report was followed by the first transhiatal robotic esophagectomy in 2003 and the first McKeown robotic esophagectomy with cervical anastomosis in 2004^[8,9]. Since then, numerous authors have reported the perioperative safety, efficacy, and potential advantages of robotic-assisted esophageal resection.

The early experience with RAMIE suggested an increased incidence of complications, including anastomotic leaks and conduit loss^[10-13], compared to open and traditional MIE approaches. The more recent literature, however, has shown a complication profile comparable to MIE^[2,14,15]. This evolution in outcomes following RAMIE is likely due to the steep learning curve associated with the introduction of a new technology, especially for a complex operation such as esophagectomy. Improvements over time may also be attributable to the adoption of structured protocols for the teaching and proctoring of robotic operations intended to enhance surgeon proficiency and safety^[16].

This review will focus on the technical details of performing and outcomes following 2-field, 3-field, and transhiatal RAMIE, including recent and ongoing studies, as well as potential future trends.

INDICATIONS FOR SURGERY

The indications for RAMIE are the same as for open esophagectomy or traditional MIE, including esophageal cancer, Barrett's esophagus with high-grade dysplasia (unamenable to, or having failed, endoscopic therapy), recalcitrant esophageal stricture, and end-stage achalasia. A contraindication to RAMIE is the presence of extensive thoracic or abdominal adhesions that preclude a minimally invasive approach. In addition, if the stomach has been resected or its vascularity interrupted by prior surgery, an alternate esophageal replacement conduit, such as the colon or jejunum, may be required. An open operation may be necessary in such cases, as the experience with robotic approaches to utilizing conduits other than the stomach is limited.

TWO-FIELD RAMIE (IVOR LEWIS RAMIE)

Patient positioning and abdominal port placement

An Ivor Lewis RAMIE is started with the patient supine. Four robotic ports (one 12 mm and three 8 mm) are typically employed as seen in [Figure 1A](#). A 12 mm right upper quadrant port is needed to create a gastric conduit with the use of a robotic stapler. The abdomen is entered with either a Hassan or Optiview technique using a 0-degree, 5 mm camera in the left upper quadrant. This port is later converted to an 8 mm robotic port. Once the peritoneal cavity is entered, carbon dioxide is insufflated to a sustained pressure of 15 mmHg. The remaining ports are placed under direct visualization. Three other robotic ports (one 8 mm midline, one 8 mm left lateral quadrant, and one 12 mm right upper quadrant) are employed. These incisions are all equidistant from the xiphoid process. A 5 mm liver retractor port can be placed either laterally in the right upper quadrant or near the subxiphoid process. Finally, an assistant port is positioned low in the pelvis, typically on the patient's right, to facilitate placement of a feeding jejunostomy in the left lower quadrant. We use a 12 mm valveless insufflation port (AirSeal; Conmed, Utica, NY) as our assistant port. It serves the dual roles of providing controlled air insufflation while being sufficiently large to allow passage of cigar-shaped sponges, topical hemostatic agents, and Penrose drains throughout the case.

Abdominal portion of the procedure

Following thorough exploration for metastatic disease, abdominal dissection begins by creating the gastric conduit. The right gastroepiploic artery is identified within the greater omentum [[Figure 1B](#)]. Starting at the level of the pylorus, the gastrocolic ligament is divided along the greater curvature of the stomach using

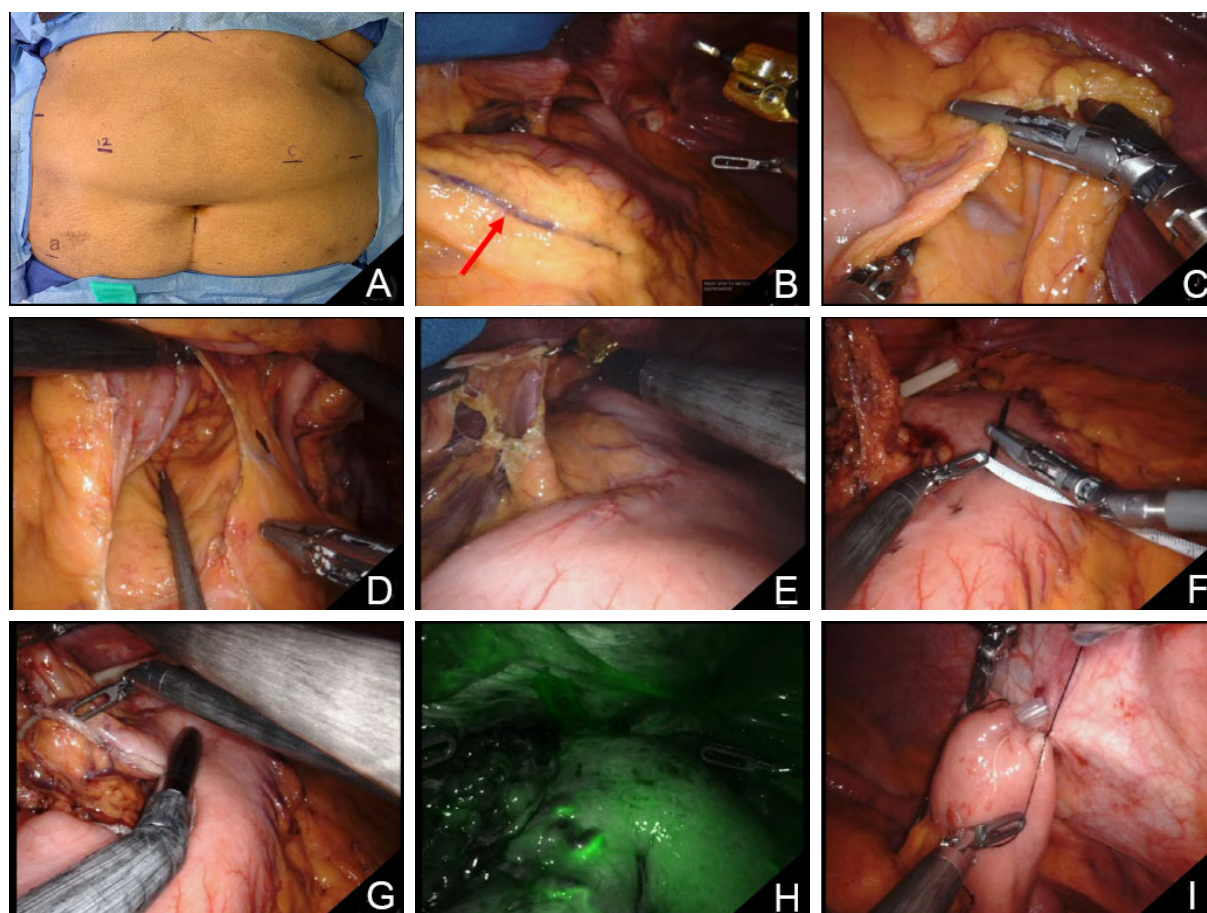


Figure 1. Abdominal portion of robotic Ivor Lewis esophagectomy. A depiction of abdominal robotic port placement is demonstrated [A: (c) camera port; (a) assistant port]; first, the right gastroepiploic arcade is defined (B, red arrow); the greater omentum is then divided and dissection proceeds along the short gastric vessels (C); once the left crus is defined, the stomach is rotated and retrogastric attachments are divided (D); the gastrohepatic ligament is divided (E) and the right crus is defined; a 4-5 cm gastric conduit is created (F) with serial firing of staplers (G); indocyanine green can be used to define the vascularity of the conduit (H); finally, a jejunostomy feeding tube is placed in the left lower quadrant (I) prior to abdominal closure

a robotic vessel sealer, taking care to preserve the right gastroepiploic arcade. Once the right gastroepiploic trunk tapers proximally along the greater curvature, the dissection plane is moved closer to the stomach and the short gastric vessels are ligated [Figure 1C]. After division of the gastrocolic ligament in its entirety, posterior dissection of the stomach is completed [Figure 1D]. The left and right crura are identified and the overlying peritoneum is dissected and swept towards the specimen. The pars flaccida (gastrohepatic ligament) is divided, taking care to preserve any accessory branches of the left hepatic artery, if sizeable [Figure 1E]. The left gastric artery is identified, nodes at its base are swept up with the specimen, and the vessel is transected flush against the celiac axis using a robotic curved tip vascular white load stapler. As mediastinal dissection is performed, a Penrose drain may be placed around the lower esophagus for later retrieval from the chest.

Next, a gastric conduit is created by dividing the lesser curvature of the stomach. A ruler may be used by the surgeon to measure a 4-5 cm transverse diameter conduit [Figure 1F], and then created with serial firings of blue- or green-load 45 mm robotic staplers. The gastric conduit is not transected in its entirety from the proximal stomach until further dissection is performed in the chest [Figure 1G]. Maintaining a connection between the specimen and the conduit allows the latter to be delivered into the mediastinum in the proper orientation as the esophagus is brought out through a subsequent chest incision. Using

the near-infrared imaging mode on the robotic console, indocyanine green (ICG) may be administered intravenously (IV) to define the vascularity of the conduit [Figure 1H]. The literature is equivocal on the use of ICG, as there is no conclusive evidence demonstrating decreased anastomotic leak rates with this strategy^[17,18]. We typically use 5 mg of ICG injected IV by the anesthesia team followed by a saline flush. The vascular arcade is analyzed using the near-infrared imaging within one minute after injection. A stitch is placed at the transition point where a loss of perfusion is noted in the gastric conduit. A Heineke-Mikulicz pyloroplasty is performed routinely by opening the anterior aspect of the pylorus longitudinally and closing it transversely using running 2-0 Ethibond stitches (Ethicon Inc., Somerville, NJ). The suture line is buttressed with a tongue of omentum. A 12-14 Fr feeding jejunostomy tube is placed in the proximal jejunum and brought out to the skin through a small incision in the left anterior abdominal wall [Figure 1I].

Thoracic portion of the procedure and anastomotic development

After completion of the abdominal phase, the patient is reintubated with a double lumen endotracheal tube and placed in the left lateral decubitus position. Single lung ventilation is established in the left lung. Four robotic ports are used to facilitate thoracic mobilization of the esophagus in addition to a fifth valveless insufflation assistant port [Figure 2A]. Three robotic ports are placed in the eighth intercostal space starting anterior to the anterior axillary line (12 mm), posterior axillary line (8 mm), and posteriorly approximately 2 cm away from the spine (8 mm). An 8 mm robotic port is placed in the third or fourth intercostal space anteriorly to allow for upper esophageal mobilization. An assistant 12 mm valveless insufflation port is placed low in the pleural cavity at about the tenth intercostal space at the level of the diaphragm. The chest is typically insufflated with carbon dioxide to a pressure of 8-10 mmHg.

Using a curved bipolar instrument, circumferential esophageal mobilization is performed starting from the level of the hiatus, proceeding superiorly to the level of the azygos vein. Starting at the inferior pulmonary ligament [Figure 2B], all paraesophageal lymphoid tissue is either removed serially during the dissection or included with the surgical specimen. Any subcarinal nodal tissue is also dissected; the bronchus intermedius is typically skeletonized in the process [Figure 2C]. The abdominal Penrose drain is retrieved and pulled into the chest, ensuring circumferential dissection of the esophagus [Figure 2D]. After mobilization of the esophagus towards the thoracic inlet, the azygos vein is divided near the superior vena cava (SVC) using a white vascular load curved tip robotic stapler [Figure 2E].

Once esophageal dissection is completed, the esophagus is divided approximately 2-3 cm superior to the azygos vein [Figure 2F] and the gastric conduit is pulled into the chest [Figure 2G]. The proximal esophageal margin is sent for frozen section analysis to ensure that it is negative for metaplasia, dysplasia, or malignancy [Figure 2H]. A 28 mm end-to-end anastomotic (EEA) stapler anvil is inserted into the proximal esophagus after removing any staples placed during transection. Running 3-0 vicryl (Ethicon, Somerville, NJ) "baseball stitch" sutures are positioned around the esophageal edge to secure the anvil in the proximal esophagus. An additional reinforcing purse string suture may be employed to assure mucosal apposition around the stem of the anvil during deployment of the stapler. Alternatively, a transoral anvil (OrVilTM, Medtronic, Mansfield, Massachusetts) may be passed through the proximal esophageal staple line [Figure 2I]. The posterior axillary line port is extended into a 4-5 cm access incision to facilitate completion of the anastomosis (either intracorporeal or extracorporeal; in our case, extracorporeal anastomosis was performed). Using a soft tissue Alexis retractor, this incision can be opened further. A gastrotomy is then created in the proximal conduit tip, and the EEA stapler is introduced through it. Once in appropriate position to engage with the anvil without excessive redundancy in the conduit, the stapler spike is brought out of the greater curvature of the conduit at or below the transition stitch. After appropriate alignment, the stapler is docked onto the anvil and fired, creating the anastomosis. Two mucosal "rings", one esophageal and one gastric, are confirmed in the EEA stapler once it is removed from the thoracic cavity.

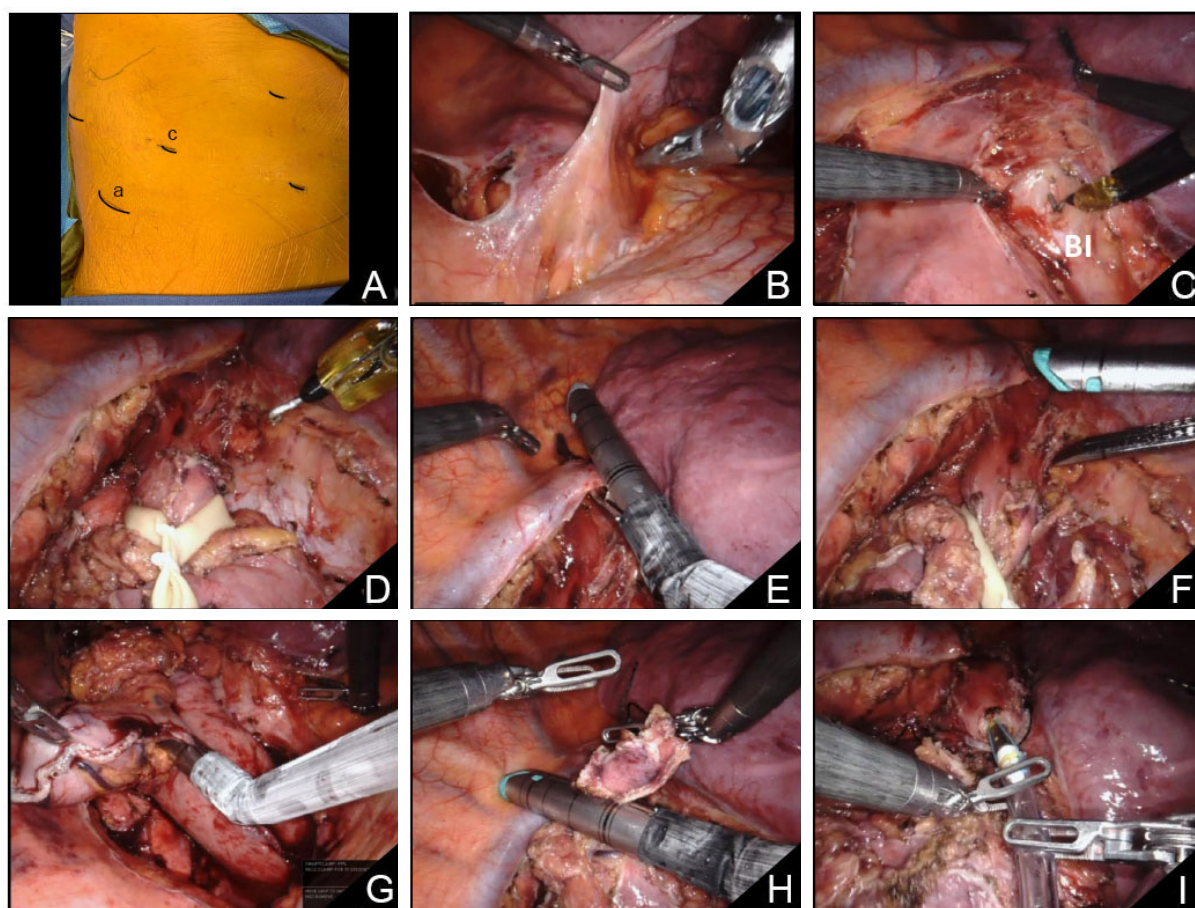


Figure 2. Thoracic portion of robotic Ivor Lewis esophagectomy. Robotic ports are placed in the right chest as shown [A: (c) camera port; (a) assistant port]; dissection in the chest typically begins with division of the inferior pulmonary ligament (B) followed by circumferential dissection of the esophagus (C) to allow placement of a Penrose drain around it (D); if performing the operation for an esophageal malignancy, nodal tissue is swept up with the specimen; the airway will be visualized during the dissection (BI). The azygos vein is divided flush with the cava (E) and the esophagus is transected superior to the azygos (F); the gastric conduit is delivered into the chest (G); and the proximal esophageal margin is checked in malignant cases (H); a transoral anvil is then delivered through the esophageal staple line (I) and an end-to-end anastomotic stapler used to complete the anastomosis, performed extra-corporeally here (images not captured). BI: bronchus intermedius

A nasogastric tube is carefully advanced beyond the anastomosis and the gastrotomy site is resected using an endoscopic gastrointestinal anastomosis (GIA) stapler. After creation of the anastomosis, a soft tissue drain is placed adjacent to the conduit, and a chest tube is placed in the pleural cavity, prior to re-inflating the right lung under direct visualization and closure.

Of note, the esophagogastric anastomosis can be performed in any of several different manners, including a linear side-to-side (functional end-to-end) stapled or a completely sewn 2-layer technique. No particular method has proven superior in terms of anastomotic leakage, though stapled anastomoses appear to lead to fewer strictures than ones that are completely sewn^[19,20].

THREE-FIELD RAMIE (MCKEOWN RAMIE)

Patient positioning and port placement

McKeown RAMIE is started with esophageal dissection in the chest. A double lumen endotracheal tube is placed and the patient is rotated to the left lateral decubitus position. The lung is isolated and four robotic ports are used for esophageal mobilization with or without an assistant port, similar to the thoracic phase

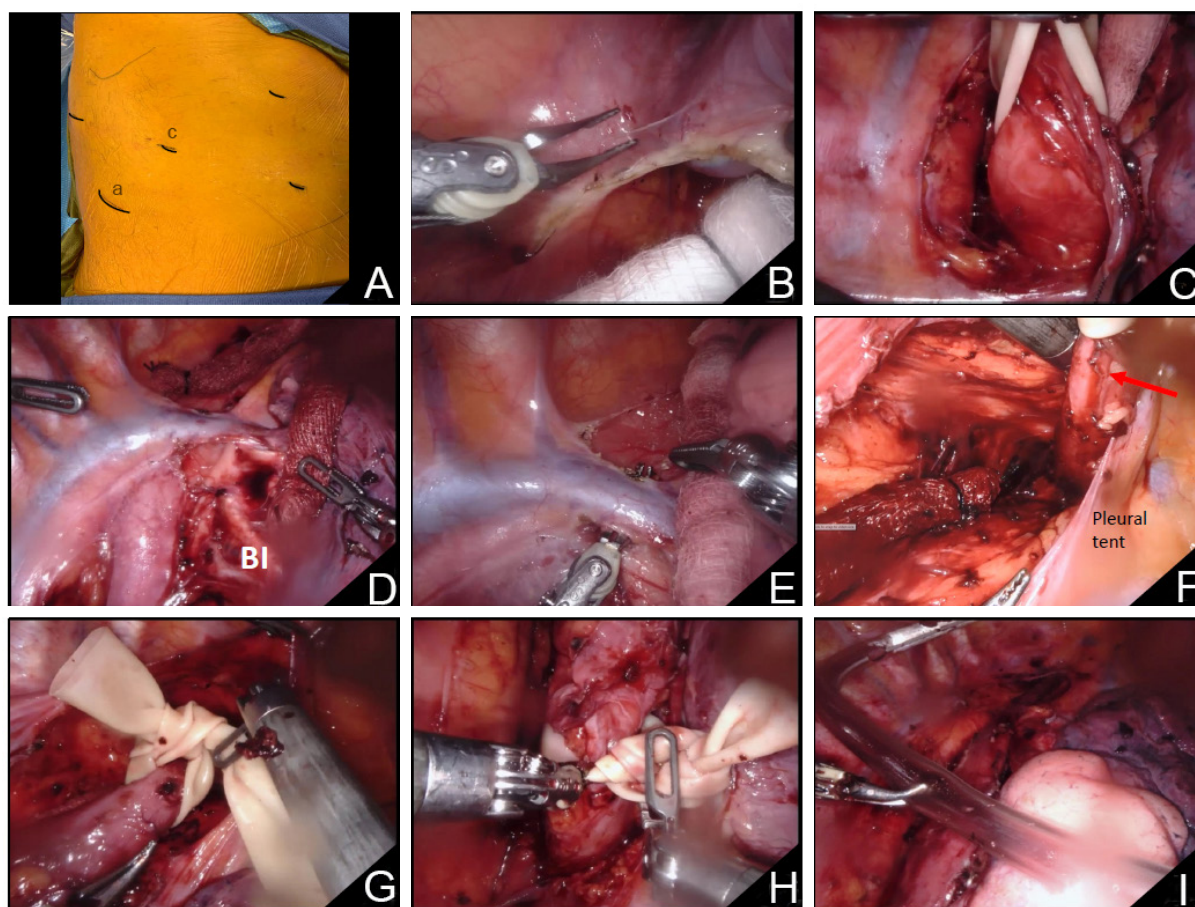


Figure 3. Thoracic portion of robotic McKeown esophagectomy. Once the ports are placed [A: (c) camera port; (a) assistant port] and the robot is docked, dissection begins at the inferior pulmonary ligament (B); as the dissection is carried *en bloc* superiorly, a Penrose drain is placed around the esophagus (C) to aid in retraction. The airway is visualized during skeletonization for cases of malignancy (D; BI); the azygos vein (E) is divided, and dissection is carried up to the apex with creation of a pleural tent (F, red arrow pointing towards the mobilized esophagus). One Penrose drain is tucked at the apex (G) while another is tucked at the diaphragm (H) prior to closing the chest (I). BI: bronchus intermedius

of an Ivor Lewis esophagectomy [Figure 3A]. Three robotic ports are placed in the eighth intercostal space - one anterior to the anterior axillary line (12 mm), another at the posterior axillary line (8 mm), and another (8 mm) posteriorly approximately 2 cm from the spine. An 8 mm robotic port is placed in the third or fourth intercostal space anteriorly to facilitate upper esophageal mobilization. An assistant 12 mm valveless insufflation port is placed low in the pleural cavity at approximately the tenth intercostal space and the chest is insufflated to a pressure of 8-10 mmHg.

Thoracic portion of the procedure

Dissection starts at the inferior pulmonary ligament and proceeds posteriorly along the esophagus [Figure 3B]. The esophagus is dissected circumferentially along with para-esophageal lymphoid tissue. A Penrose drain is placed circumferentially around the esophagus to aid superior and inferior mobilization [Figure 3C]. The airway is skeletonized in the process [Figure 3D]. Care must be taken not to injure the thoracic duct; if there is doubt, the duct should be clipped or ligated. The azygos vein is divided near the SVC using a curved tip vascular load placed through the anterior port [Figure 3E]. The previously placed Penrose drain is positioned in the apex of the chest for retrieval from the neck [Figure 3F and G]. A second Penrose drain can be placed at the level of the diaphragm for later retrieval from the abdomen [Figure 3H]. After ensuring adequate hemostasis, a chest tube is placed through the anterior incision and advanced to the apex [Figure 3I]. The lung is then re-inflated under direct visualization before closing the incisions.

Abdominal dissection

The patient is positioned supine and the double lumen endotracheal tube is switched to a single lumen tube. The patient's neck is extended and turned slightly to the right, exposing the left lower anterior neck. The neck, anterior chest, and abdomen are prepped and draped in routine sterile fashion. The abdominal ports are placed as for an Ivor Lewis RAMIE [Figure 4A]. Four robotic ports (one 12 mm and three 8 mm) are typically employed; a 12 mm right upper quadrant port is needed to create a gastric conduit with the use of a robotic stapler.

The abdomen is entered with either a Hassan or Optiview technique with a 0-degree, 5 mm camera in the left upper quadrant. This port is later converted to an 8 mm robotic port. Once in the peritoneum, the abdomen is insufflated with carbon dioxide to a pressure of 15 mmHg. Three additional robotic ports (one 8 mm midline, one 8 mm left lateral quadrant, and one 12 mm right upper quadrant) are placed under direct visualization. These ports are placed equidistant from the xiphoid process. A 5 mm liver retractor port can be employed either laterally in the right upper quadrant or near the subxiphoid process. Finally, an assistant 12 mm valveless port is placed low in the pelvis typically on the patient's right side, in order to facilitate placement of a feeding jejunostomy in the left lower quadrant.

The dissection is started with creation of the gastric conduit. The gastrocolic ligament is divided along the greater curvature of the stomach with a robotic vessel sealer while preserving the right gastroepiploic arterial arcade [Figure 4B]. Once the right gastroepiploic trunk tapers proximally along the greater curvature, the dissection plane is moved closer to the stomach and the short gastric vessels are divided [Figure 4C]. Next, posterior dissection of the stomach is completed [Figure 4D], and the peritoneum over the left and right crus is stripped and swept away with the surgical specimen. Dissection is continued into the mediastinum until the inferior Penrose drain, placed during the thoracic phase of the procedure, is encountered and delivered into the surgical field.

The left gastric artery is identified and divided using a robotic vascular stapler. The pars flaccida is divided, and a 4-5 cm gastric conduit is created [Figure 4E] with serial firings of the robotic 45 mm blue or green load staplers [Figure 4F]. Additional conduit length can be achieved by gently stretching the stomach longitudinally as the robotic stapler is fired. Using near-infrared imaging, IV ICG can be administered to allow identification of the transition point of perfusion along the conduit. A stitch can be placed to mark this point, guiding creation of the esophagogastric anastomosis at a region of adequate gastric perfusion [Figure 4G]. Lastly, the conduit is marked to ensure delivery of the conduit to the neck without torsion as it is pulled up through the mediastinum [Figure 4H].

Our practice is to perform a pyloric drainage procedure. A Heineke-Mikulicz pyloroplasty is completed as described previously and buttressed with a tongue of the omentum [Figure 4I]. A Kocher maneuver may be performed if the pylorus does not reach the diaphragmatic hiatus. A 12-14 Fr feeding jejunostomy is placed in the proximal jejunum and brought out to the skin in the left lower quadrant.

Left cervical dissection and anastomotic development

A five cm oblique incision is made anterior to the left sternocleidomastoid (SCM) muscle extending cephalad from the sternal notch. The platysma is divided and the left SCM is retracted laterally. Using electrocautery, the left omohyoid muscle is transected and the strap muscles divided as needed to provide exposure of the cervical esophagus. The left inferior thyroid artery may need to be clamped, divided, and ligated as it frequently impairs this exposure. Division and ligation of the vessel should be performed as far laterally as possible to avoid injury to the left recurrent laryngeal nerve (RLN). Injury to this nerve is also prevented by avoiding electrocautery and placement of either metal pickups or retractors in the region of the left tracheo-esophageal (TE) groove. The assistant's index finger, rather than a metal retractor, is

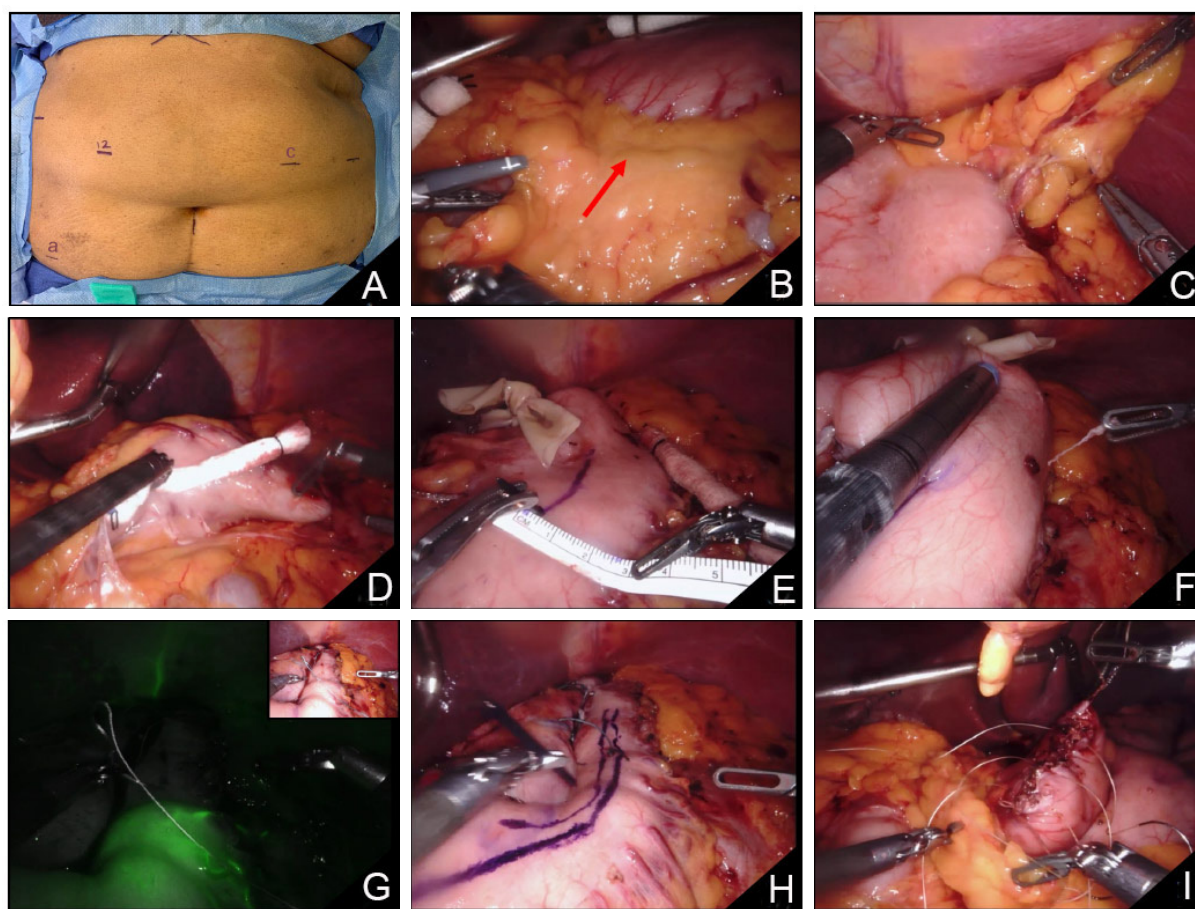


Figure 4. Abdominal portion of robotic McKeown esophagectomy. Four robotic ports are placed, along with a liver retractor in the right upper quadrant and assistant port in the right lower quadrant [A: (c) camera port; (a) assistant port]; next, the greater omentum is divided after identifying the right gastroepiploic arcade (B, red arrow) and the dissection is carried up to the short gastric vessels (C); the stomach is rotated to the right and posterior attachments are divided (D); after ensuring circumferential dissection of the conduit, the mediastinal Penrose drain is delivered into the field (E); a 4-5 cm gastric conduit is created (E and F) and indocyanine green testing of the conduit is conducted prior to transecting the stomach (G); a transition stitch can be placed where there is a clear demarcation in perfusion (G insert); once the stomach is transected, two parallel lines are marked on the conduit to ensure that the conduit is pulled into the neck without torsion (H); a pyloric drainage procedure may be performed (I). The anastomosis is performed in the neck below the transition stitch (images not captured)

utilized to retract the trachea and improve exposure of the cervical esophagus. A Henley retractor with interchangeable blades of varying lengths is the optimal tool for facilitating exposure in the neck. A long blade attached to the Henley is used to retract the carotid sheath, and a shorter blade on the opposite arm is used to retract the strap muscles. As previously mentioned, a retractor blade should not be placed in the TE groove to prevent RLN injury. The esophagus is then mobilized in a circumferential fashion using a combination of blunt and sharp dissection. The dissection plane is kept on the surface of the esophagus, taking care to avoid the left RLN situated more anteriorly toward the trachea. Once the esophagus has been mobilized in its entirety, the apical Penrose drain that was placed during the thoracic phase of the procedure is manually palpated and delivered into the incision.

The specimen is then pulled up gradually into the neck. Direct robotic visualization from the abdomen should be performed while the conduit is carefully delivered through the mediastinum. Care must be taken to ensure that the conduit does not torque as it gets pulled up into the mediastinum. Once the conduit is completely delivered and the transition stitch is identified, either a linear side-to-side (functional end-to-end) or a completely handsewn anastomosis is performed. We prefer the former approach utilizing the GIA

stapler. The common opening may be closed with either a TA stapler or using a hand-sewn technique. A nasogastric tube is passed under direct visualization before completing the anterior wall of the anastomosis. A drain is left in the cervical bed to monitor for leaks. After placement of two 2-0 sutures securing the conduit to the diaphragm, pneumoperitoneum is reduced, and the abdominal and neck incisions closed in layers.

TRANSHIATAL RAMIE

Typically, transhiatal RAMIE is chosen for patients who have mitigating pulmonary or cardiac comorbidities and may not tolerate single-lung ventilation. Transhiatal RAMIEs can be technically challenging given the mediastinal dissection with the robot.

Patient positioning and port placement

The patient is positioned supine, with a single lumen tube, with both arms tucked. The neck is turned to the patient's right, and the left neck, chest, abdomen, and pelvis are all prepped and draped in one field. The robot is docked in the abdomen. Typically, four robotic ports (one 12 mm and three 8 mm) are employed. The 12 mm port is positioned in the right upper quadrant to allow creation of the gastric conduit with the use of a robotic stapler. The abdomen is entered either using a Hassan or an Optiview technique with a 0-degree, 5 mm camera in the left upper quadrant. This port is later converted to an 8 mm robotic port. Once in the peritoneum, the abdomen is insufflated with carbon dioxide to a pressure of 15 mmHg. Three remaining robotic ports (one 8 mm midline, one 8 mm left lateral quadrant, and one 12 mm right upper quadrant) are employed under direction visualization and are positioned equidistant from the xiphoid process. A 5 mm liver retractor port can either be placed laterally in the right upper quadrant or near the subxiphoid process. Lastly, an assistant port is positioned low in the pelvis, typically on the patient's right side, to facilitate placement of a feeding jejunostomy in the left lower quadrant.

Abdominal portion of the procedure

The abdominal portion begins with creation of the gastric conduit. Gastric mobilization starts with dividing the greater omentum and preserving the right gastroepiploic arcade. Short gastric vessels are divided, and the stomach is rotated anteriorly to allow take-down of retrogastric adhesions. Dissection is then carried over to the lesser omentum. The pars flaccida is opened and the incision extended toward the right crus. The left gastric and celiac axis nodes are swept up towards the specimen. Hiatal dissection is completed circumferentially while stripping the peritoneum off the crura.

Under direct visualization, the camera and instruments are advanced into the mediastinum for extensive mediastinal dissection. Dissection is continued as high as possible in order to facilitate mobilization of the native esophagus from the neck, which is blind otherwise.

A 4-5 cm gastric conduit is created utilizing sequential stapler fires along the lesser curve. Starting at the incisura angularis, a vascular load is first employed, followed by serial firing of blue- or green- robotic staplers while applying gentle longitudinal tension on the conduit. Once the esophagus is completely transected, the conduit is attached to the specimen for later retrieval in the neck. A Heineke-Mikulicz pyloroplasty is completed by placing stay sutures on the superior and inferior aspects of the pylorus. The pylorus is opened longitudinally and closed transversely, ensuring mucosal apposition during closure. The suture line can be covered with a tongue of omentum. A generous Kocher maneuver can be performed if the pylorus does not reach the hiatus easily to allow for tension-free delivery of the anastomotic site into the neck. A 12-14 Fr jejunostomy feeding tube is placed in the left lower quadrant.

Cervical dissection and anastomotic development

With the abdominal ports in place, attention is diverted to the left neck. A 5 cm oblique incision is made anterior to the left SCM. Dissection is carried down through the platysma using electrocautery. The

omohyoid muscle is divided, the inferior thyroid artery ligated and divided, and the strap muscles dissected to allow access to the esophagus. No cautery or metal retractors are used in the region of the TE groove to avoid inadvertent injury to the RLN. Blunt and sharp dissection is performed circumferentially around the cervical esophagus. If dense adhesions are encountered at the thoracic inlet, a mediastinoscope can be employed via the cervical incision to facilitate adhesiolysis under direct visualization. Such efforts allow precise dissection and prevent inadvertent injury to the azygos. Next, the specimen and conduit are pulled into the neck in proper orientation, and the stomach is divided at or below the transition stitch. The proximal and distal margins are checked for metaplasia, dysplasia, or malignancy prior to completing the anastomosis.

The anastomosis is performed either in a completely hand-sewn fashion or by utilizing a hybrid technique, whereby the posterior aspect is started with a GIA stapler and the common opening is closed anteriorly in a hand-sewn fashion. A nasogastric tube is passed under direct visualization prior to closing the anterior wall. A drain is placed in the neck to monitor for leaks. The conduit is then tacked to the crura with two 2-0 Ethibond sutures. After ensuring hemostasis, pneumoperitoneum is released, and all incisions are closed in layers.

POSTOPERATIVE COURSE

After surgery, the patient is admitted to an intensive or intermediate care unit for one to two days and stepped down to a regular surgical unit once clinically stable. Enteral feeds are started via the feeding jejunostomy tube on postoperative day 1 and advanced to goal over the course of the next few days. The nasogastric tube is discontinued after return of bowel function and when output is at an acceptably low level. The chest tube is typically removed on postoperative day 4 or 5, depending on the volume and character of drainage. The patient is discharged once they have reached their benchmarks and are tolerating goal tube feeds. The patient is kept NPO until a swallow study is performed as an outpatient on postoperative day 14. This protocol promotes early discharge while allowing small, clinically insignificant anastomotic leaks to seal.

LYMPH NODE DISSECTION IN RAMIE

The extent of lymph node dissection has been an important topic in the thoracic surgical literature. Unlike resections for colorectal cancer, no definite cut-off has been established to define adequate lymph node harvest for esophageal or esophagogastric junction carcinoma; different reports have determined varying thresholds. Of importance is the fact that the aggregate lymph node count does not take into consideration the location of the nodal basins harvested, such as whether they are in the abdomen, chest, or neck. A better measure of the adequacy of lymphadenectomy, therefore, is the rate of locoregional recurrence following esophagectomy by the various approaches.

Recent large cohort studies have found an average harvest of 25-29 regional nodes during RAMIE^[15,21,22]. Rates of locoregional recurrence, however, are not well defined, as the studies do not differentiate local and distant recurrences when determining disease-free survival. When compared to open or traditional MIE, locoregional recurrence rates following RAMIE have been reported to be comparable or lower^[5,23]. Robotic surgical platforms may offer advantages in dissection along the RLN in the apex of the chest, performed with the patient in either the prone or lateral decubitus position^[24,25]. A number of publications have also confirmed the lower incidence of RLN neuropraxia and vocal cord paralysis with RAMIE when compared to traditional MIE^[26,27].

DISCUSSION

With increasing exposure to robotic surgical techniques and with continual improvements in robotic design and technology, including the introduction of robotic staplers and energy devices, the number of

robotic cancer operations is on the rise^[28,29]. A major advantage of current robotic systems, compared to the performance of an open esophagectomy, is the seven degrees-of-freedom in the wristed instruments, allowing the surgeon to operate ergonomically with angulation comparable to the human wrist. This dexterity allows the surgeon to complete esophageal and nodal dissections similar to an open procedure, facilitates intracorporeal suturing and knot tying, and enhances the surgeon's ability to operate in difficult-to-reach places such as the apex of the chest, subcarinal space, and splenic flexure. The additional advantages of current robotic platforms include three-dimensional visualization, 10-fold magnification, and a 6-Hertz motion filter designed to eliminate tremor. In addition, robotic surgical platforms offer longer instruments compared to other minimally invasive systems with a fixed fulcrum supported by robotic arms, potentially leading to reduced stress on the chest and abdominal wall. An operating console for a second surgeon is used in some robotic operating rooms, allowing surgeons to perform surgery in tandem with, and facilitating training in a dynamic and supportive manner.

Given these advantages, the increasing utilization of surgical robotics in the performance of esophagectomy should come as no surprise. While the initial experiences with RAMIE were associated with higher complication rates, subsequent reports have shown that RAMIE can be performed with superior perioperative outcomes, and equivalent oncologic survival when compared to open and traditional minimally invasive approaches^[14,15]. Such experiences suggest that the potential disadvantages of current surgical robots, including the lack of haptic feedback and the positioning of the surgeon at a remote console in a non-sterile environment, can be mitigated by surgeon experience and the presence of trained assistants in the sterile field. The incidence of associated complications, such as major uncontrolled hemorrhage, appears to be at an acceptably low level.

Ongoing studies about RAMIE

Numerous retrospective studies have supported the role of MIE and RAMIE when compared to open esophagectomy. Only a limited number of prospectively designed, randomized controlled trials (RCTs), however, have been reported to date. An RCT of 115 patients from 5 European centers (the TIME trial) evaluated the outcomes of 59 patients randomly assigned to MIE compared to 56 patients randomized to open esophagectomy. Initial results were published in 2012, and long-term results in 2017^[1,4]. While the baseline demographics and clinical characteristics were similar in both groups, the overall 3-year survival was higher in the MIE group (50.5% vs. 40.4%), although the difference was not statistically significant ($P = 0.207$). Disease-free 3-year survival rates were also similar between the two groups [40.2% for MIE, 35.9% for open; HR = 0.691 (95%CI: 0.389-1.239)]. Of note, pulmonary complications were significantly lower in the MIE group (12% vs. 34%, $P = 0.005$), as was blood loss (200 mL vs. 475 mL, $P < 0.001$) and hospital stay (11 days vs. 14 days, $P = 0.044$) despite conversions from MIE to open in eight cases. The anastomotic leak rate, re-operative rates, and 30-day mortality rates were similar between groups.

The ROBOT trial, published in 2019, was an RCT from a single institution in the Netherlands^[5]. Patients with esophageal cancer were randomized to RAMIE ($n = 54$) or open esophagectomy ($n = 55$). Findings were similar to those from TIME, with less overall surgery-related complications following RAMIE (59% vs. 80%; $P = 0.02$), fewer pulmonary complications (32% vs. 58%; $P = 0.005$), and a lower incidence of atrial fibrillation (22% vs. 46%, $P = 0.01$). On the contrary, no differences were noted in anastomotic leak rates or mortality rates between the two groups. Median ICU stay, hospital stay, R0 resection rates, and lymph node retrieval numbers were not significantly different between the two groups. Functional recovery, patient reported pain scores, and short-term quality of life assessments all favored the RAMIE approach. Overall, the study found improved short-term outcomes following robotic esophagectomy compared to the open approach.

While several retrospective studies, as well as these RCTs, have compared both MIE and RAMIE to open esophagectomy, no studies have compared RAMIE to MIE. A recently opened trial (RAMIE trial) is

designed to compare RAMIE to MIE in a randomized controlled setting^[30]. The study includes four centers from China and will focus on patients with esophageal squamous cell carcinoma (SCC). The primary endpoint of the study is 5-year overall survival, with secondary endpoints of 3-year overall and disease-free survival, 5-year disease-free survival, short-term outcomes, and quality of life. The hypothesis of the trial is that RAMIE will result in equivalent oncologic outcomes and long-term quality of life, along with shorter operative times, lower perioperative complications, and shorter hospital stays, when compared to MIE.

The REVATE trial, a two-center, open-label RCT of esophageal SCC, will compare lymph node dissection along the RLN during RAMIE vs. MIE^[25]. The two institutions participating in this RCT are from China and Taiwan, where SCC is more prominent than esophageal adenocarcinoma, favoring upper or middle esophageal tumors where dissection of lymph nodes around the RLNs is critical. The study, while meaningful for that patient population, will be difficult to apply to Western cohorts comprised primarily of patients with adenocarcinoma of the distal esophagus or esophagogastric junction.

CONCLUSION

Robotic approaches to esophagectomy are being utilized with increased frequency and improve upon established techniques of MIE by offering superior dexterity, maneuverability, ergonomics, and visualization. Randomized and non-randomized studies have demonstrated equivalent oncologic outcomes between robotic and open esophagectomies, with superior results for the robotic approach in terms of hospital stay, postoperative morbidity, and overall quality of life. As surgeons become trained in robotic techniques and implement them further into their treatment armamentarium, the use of RAMIE for appropriately selected cases of esophageal malignancy or other end-stage esophageal disease will undoubtedly, continue to increase. With the introduction of novel and competing robotic technologies, the hope is that their cost will decrease, allowing further penetration into the marketplace.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the manuscript, and performed data analysis and interpretation: Khaitan PG

Contributed to manuscript writing and editing: Lazar JF, Henderson HR, Watson TJ

Provided technical and material support: Margolis M

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Echocardiographic evaluation of mitral valve regurgitation

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Abstract

Echocardiography is the primary imaging modality for the evaluation of mitral valve regurgitation. A comprehensive assessment of mitral regurgitation using different echocardiographic techniques provides important information regarding the etiology and severity of mitral regurgitation and its consequences on cardiac function. In addition, echocardiography plays an important role in the management of patients with mitral regurgitation.

Keywords: Echocardiography, mitral valve, mitral regurgitation, severity

INTRODUCTION

Echocardiography is the gold standard diagnostic test for the evaluation of valvular heart disease, particularly mitral regurgitation (MR)^[1]. An accurate assessment of MR severity is vital for clinical decision-making. Two-dimensional (2D) and three-dimensional (3D) echocardiography are mainly used to identify the etiology and mechanism of MR, while Doppler techniques provide accurate assessment of MR severity. In addition, integration of other supportive findings such as size and function of the left ventricle (LV), coexistence of significant tricuspid regurgitation and pulmonary artery pressure play an important role in the decision-making process regarding the type and time of intervention for severe MR^[2]. In this article, we will discuss in detail the role of echocardiography in the evaluation of MR.



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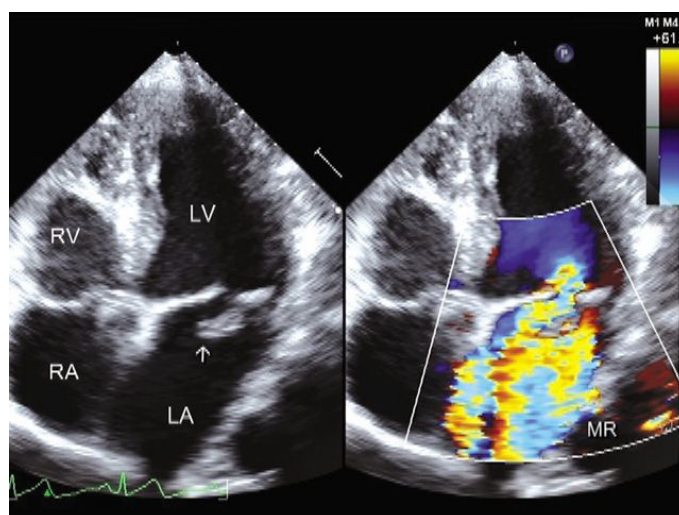


Figure 1. Two-dimensional transthoracic echocardiography demonstrates a myxomatous mitral valve and prolapse of posterior mitral leaflet (arrow) with severe MR. RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium; MR: mitral regurgitation. Reproduced with permission from Manjunath *et al.*^[4]

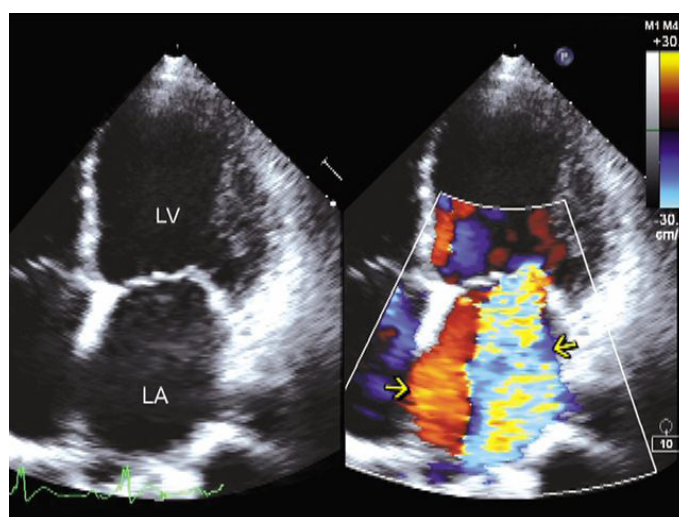


Figure 2. Two-dimensional transthoracic echocardiography in apical four-chamber view shows a dilated LV with mitral valve coaptation point displaced into the LV and severe MR. LV: left ventricle; LA: left atrium; MR: mitral regurgitation. Reproduced with permission from Manjunath *et al.*^[4]

ASSESSMENT OF ETIOLOGY AND MECHANISM OF MR

Understanding the complex anatomy of the mitral valve (MV) is essential for accurate assessment of MR. The MV apparatus consists of mitral annulus, MV leaflets, chordae tendineae, papillary muscles and the underlying ventricular wall. Pathological abnormality of any one of these components can lead to MR [Figure 1]^[3,4]. For instance, MR can occur due to primary (degenerative) MV disease affecting the MV leaflets and/or chordae tendineae, while secondary MR occurs due to a pathological process of the LV or left atrium (LA) [Figure 2]^[4,5]. In case of ventricular disease, due to either ischemic or non-ischemic cardiomyopathy, MR occurs due to regional or global remodeling of the LV, which causes lateral displacement of papillary muscles, resulting in annular dilation and leaflet tethering. However, there are some differences in the mechanism of MR in these two types of cardiomyopathy. The main mechanism for secondary MR in ischemic cardiomyopathy occurs due to inferior wall motion abnormalities, leading

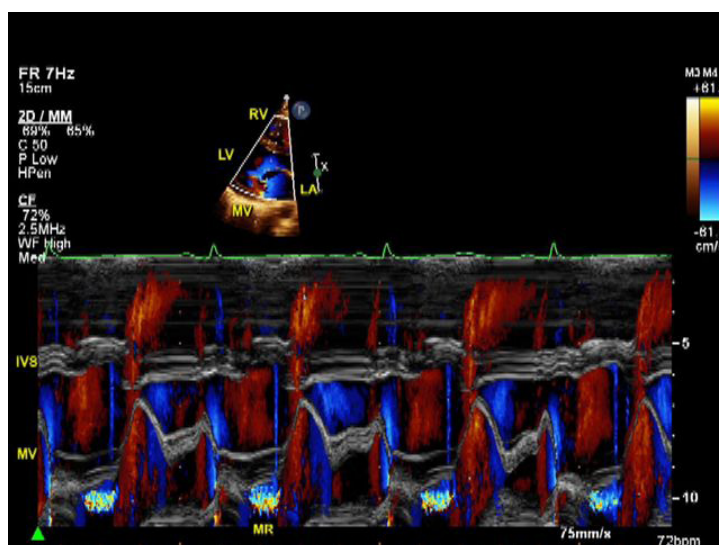


Figure 3. M-mode transthoracic echocardiogram in the parasternal long-axis view shows mid to late systolic MR in a patient with MV prolapse. IVS: interventricular septum; MR: mitral regurgitation; MV: mitral valve; LV: left ventricle; LA: left atrium; RV: right ventricle. Copyright with Aiman Smer

to systolic restriction and tethering of the posterior MV leaflet. This asymmetrical tenting pattern of the MV leaflets usually leads to posteriorly directed MR^[6]. In contrast, non-ischemic secondary MR is usually associated with global wall motion abnormalities, leading to equal displacement of papillary muscles and annular dilation, which results in symmetrical tethering of both leaflets leading to central MR^[7].

Atrial fibrillation is another common cause of secondary MR, termed atrial MR. In patients with chronic atrial fibrillation, severe LA enlargement and annular dilation can lead to incomplete coaptation of the MV leaflets. Atrial remodeling of the mitral annulus can also lead to posterior displacement of the mitral annulus and tethering of the posterior MV leaflet^[8]. In addition, myocardial dyssynchrony due to left bundle branch block or right ventricular pacing can potentially predispose to MR by a decrease in MV closing forces and dyssynchronous papillary muscle function^[9].

M-MODE ECHOCARDIOGRAPHY

M-mode was one of the earliest echocardiographic techniques to evaluate MV abnormalities^[10]. The high temporal resolution of M-mode allows accurate diagnosis of the mechanism of MR in patients with MV prolapse and MR induced by hypertrophic obstructive cardiomyopathy. Adding color Doppler M-mode improves its diagnostic accuracy and helps determine whether MR is holosystolic or mid or late systolic [Figure 3]. This is an important aspect to consider since MR severity may be overestimated when using standard 2D/color Doppler imaging criteria of severity such as MR jet area, jet area/LA size ratio and proximal jet convergence and vena contracta (VC) size, because they do not take into account the duration of MR.

2D ECHOCARDIOGRAPHY

2D transthoracic echocardiography (TTE) is the primary diagnostic test for the initial detection of MR and assessing its severity as well as evaluating the etiology and mechanism of MR [Table 1]. 2D echocardiography can easily differentiate between primary MR due to MV prolapse or ruptured chord versus secondary (functional) MR due to dilated LV. This anatomic assessment of the MV and LV in terms of morphology and function, can be particularly useful in determining whether percutaneous or surgical MV repair should be considered. The transthoracic parasternal long- and short-axis views of MV allow

Table 1. Etiology and mechanism of mitral regurgitation

Etiology of mitral regurgitation	Mechanism of mitral regurgitation
Atrial fibrillation	Annular dilation, leaflet mal-coaptation
Acute ischemia	Papillary muscle dysfunction or rupture
Congenital or genetic disorders; Marfan syndrome, Ehlers-Danlos syndrome, Down syndrome	Leaflet prolapse, cleft or rudimentary leaflets
Endocarditis; infective and marantic	Leaflet perforation, mal-coaptation, chordal rupture
Drugs; fenfluramine and dexfenfluramine	Leaflets, chordae
Functional/secondary; dilated cardiomyopathy	Left ventricular remodeling, papillary muscle displacement leading to leaflet tethering and annulus dilation
Hypertrophic obstructive cardiomyopathy	Systolic anterior motion of anterior mitral valve leaflet
Myxomatous degeneration (primary)	
(1) Barlow's disease	Leaflets prolapse
(2) Fibroelastic deficiency	Rupture chordae
Mitral annular calcifications	Annulus, leaflets
Rheumatic heart disease	Leaflets, chordae
Radiation	Leaflets, chordae

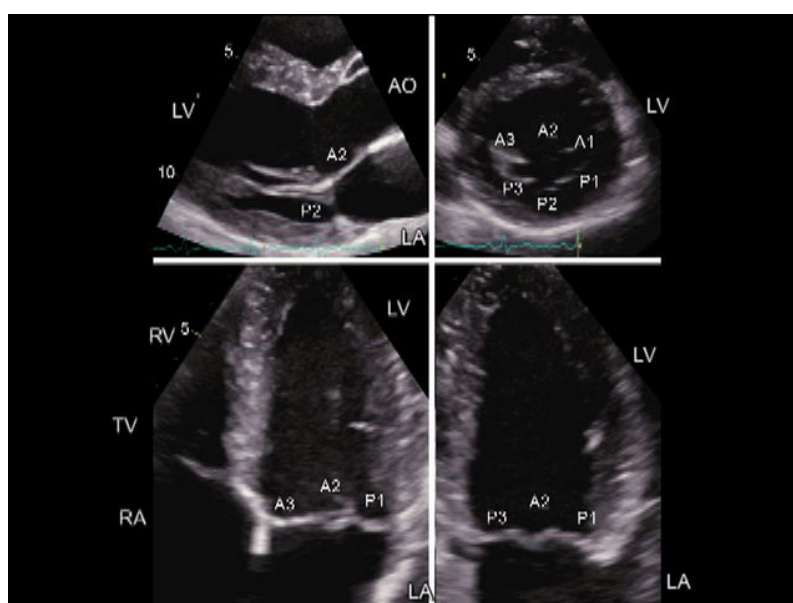


Figure 4. Mitral valve segment and scallop analysis with two-dimensional transthoracic echocardiography. Left upper panel: parasternal long-axis view depicting A2 segment and P2 scallop. Right upper panel: parasternal short-axis view permitting the assessment of A1, A2 and A3 segments and P1, P2 and P3 scallops. Left lower panel: apical four-chamber view showing A3, A2, and P1. Right lower panel: apical two-chamber view displaying P3, A2 and P1. RA: right atrium; RV: right ventricle; LV: left ventricle; LA: left atrium; TV: tricuspid valve; AO: aorta. Reproduced with permission from Pierard *et al.*^[11]

direct visualization of mitral valve scallops and leaflet motion [Figure 4]^[11]. 2D echocardiography can also accurately diagnose rheumatic MR and endocarditis-induced MR.

2D transesophageal echocardiography (TEE) is indicated for evaluation of patients with MR in whom TTE is of poor quality or provides nondiagnostic information about the mechanism and severity of MR^[2]. A jet area of 10-15 cm² signifies severe MR. The proximity to the MV apparatus and 3D capabilities of TEE allow accurate assessment of MV abnormalities. In addition, TEE can provide additional information regarding the feasibility of percutaneous intervention and the likelihood of successful surgical repair. There are several TEE parameters required to assess the suitability of transcatheter edge-to-edge clip repair (MitraClip) for patients with severe chronic MR, who are deemed high surgical risk [Table 2]^[12,13]. Echocardiographic features such as MV area, annular calcification and the number of scallops involved in MR can predict

Table 2. Echocardiographic parameters for MitraClip feasibility

	Favorable	Unfavorable	Contraindicated
Etiology of MR	Myxomatous valve disease	Severe annular dilation, > 50 mm or EROA > 70.8 mm ²	Rheumatic or endocarditis valve disease
Location of MR	Central, A2/P2 segments	Peripheral, A1/P1 or A3/P3 segments	Perforated mitral leaflets or clefts
Grasp zone			
Calcification	None	Mild	Moderate to severe
Length	> 10 mm	7-10 mm	< 7 mm
Mitral valve			
Area	> 4 cm ²	> 3.5 and < 4 cm ²	< 3.5 cm ²
Gradient	< 4 mmHg	> 4 and < 5 mmHg	> 5 mmHg
Length of posterior leaflet	> 10 mm	7-10 mm	< 7 mm
Leaflet mobility	Mobile	Restricted motion	Immobile
Primary MR	Flail gap < 10 mm Flail width < 15 mm	Flail gap > 10 mm Flail width > 15 mm	
Secondary MR	Coaptation depth < 11 mm Coaptation length > 2 mm	Coaptation depth > 11 mm Coaptation length < 2 mm	

EROA: effective regurgitation orifice area; MR: mitral regurgitation

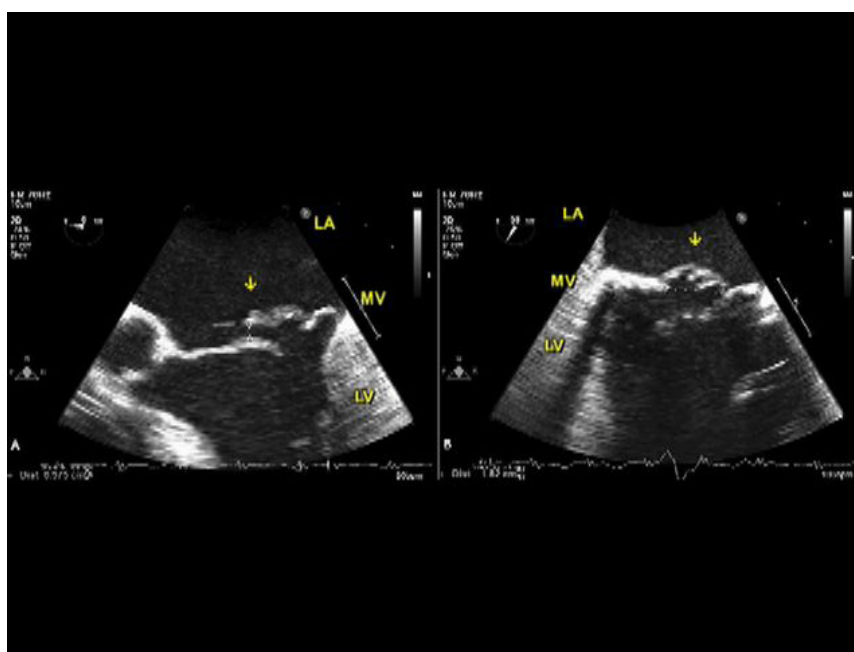


Figure 5. Two-dimensional transesophageal echocardiography demonstrates a flail MV (arrow) in five- and two-chamber views. LV: left ventricle; LA: left atrium; MV: mitral valve. Copyright with Aiman Smer

successful MitraClip placement^[14]. In primary MR, measurements of leaflet separation and flail gap and width are important for procedural success [Figure 5]. While in secondary MR, measurements of annular diameter and coaptation length and depth are essential to predict adequate leaflet grasping and successful repair [Figure 6]. In addition, TEE is essential to guide both surgical and percutaneous MV repair, immediately assess procedural success and identify potential complications.

3D ECHOCARDIOGRAPHY

3D echocardiography either from a transthoracic or transesophageal approach can provide superb images of the MV apparatus. The ability of 3D imaging to visualize the MV from different 2D angles allows accurate assessment of MR^[15]. A unique advantage of 3D TEE is the ability to provide an en face view of the MV from the LA perspective, which is similar to the surgeon's view in the operating room [Figure 7]. This view

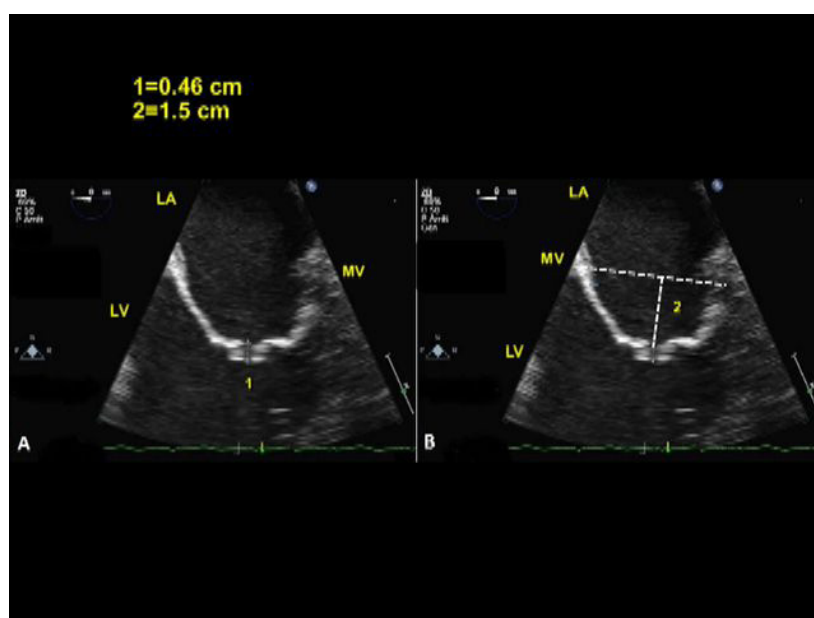


Figure 6. Two-dimensional transesophageal echocardiography demonstrates systolic non-coaptation gap (1) of the MV which is displaced into the LV. #2 represents the perpendicular distance of the MV coaptation point from the MV annulus. LV: left ventricle; LA: left atrium; MV: mitral valve. Copyright with Aiman Smer

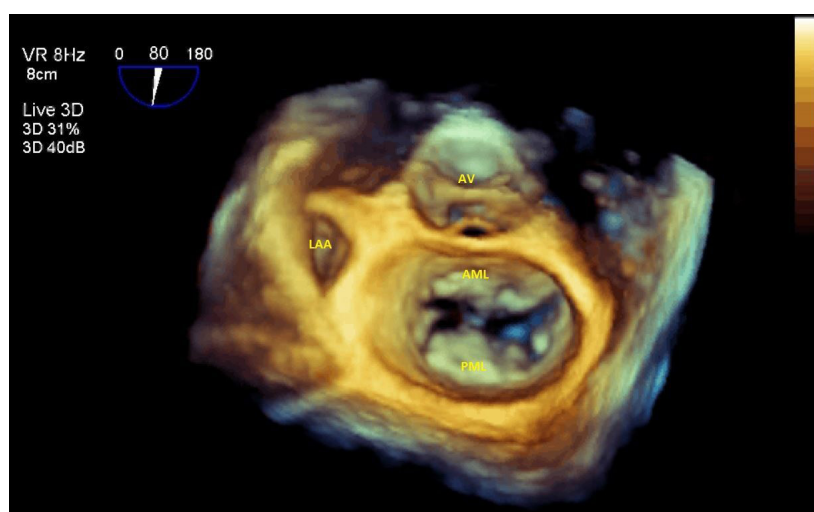


Figure 7. Live/real-time three-dimensional transesophageal echocardiography shows an en face view of the MV. MV: mitral valve; AML: anterior MV leaflet; AV: aortic valve; LAA: left atrial appendage; PML: posterior MV leaflet. Copyright with Aiman Smer

allows accurate localization of the involved MV leaflet or scallop in MR and also identify rare conditions such as MV cleft, which is very difficult to diagnose on 2D imaging. In addition, 3D echocardiography is especially useful in prosthetic MV regurgitation and guidance of percutaneous cardiac interventions. For instance, the use of real-time 3D TEE in MitraClip procedure is crucial for optimal trans-septal puncture and device placement.

In general, 2D and 3D echocardiography are mainly used to identify valve pathology and mechanism of MR. However, there are certain structural findings such as flail leaflet, ruptured papillary muscle, and large coaptation defect, which are specific for severe MR. In addition, dilated LV along with atrium with normal LV function suggests severe MR.

Table 3. Grading the severity of mitral regurgitation

	Mild	Moderate	Severe
Qualitative parameters			
MV morphology	Normal/abnormal	Normal/abnormal	Flail leaflet/chordal rupture
Color flow Doppler of MR jet*	< 20% of LA size	20%-40% of LA size	> 40% of LA size
Continuous wave Doppler			
MR jet density	Faint	Dense	Dense
MR jet contour	Parabolic	Parabolic	Early peaking-triangular
Flow convergence zone*	No or small	Intermediate	Large
Semi-quantitative parameters			
Vena contracta	< 0.3 cm	0.3-0.69 cm	≥ 0.7 cm
Mitral valve inflow	A-wave dominant		E-wave dominant, > 1.2 m/s
	Mitral to aortic TVI ratio < 1 m/s	Mitral to aortic TVI ratio 1 to 1.4 m/s	Mitral to aortic TVI > 1.4 m/s
Pulmonary veins flow	Systolic dominance	Normal or systolic blunting	Systolic flow reversal in > 1 vein
LA/LV size	Normal	Intermediate	Enlarged, particularly with normal LV function
Quantitative parameters			
Effective regurgitant orifice area by PISA or 3D color Doppler echo	< 0.2 cm ²	0.2-0.29 cm ² ; Mild to moderate 0.3-0.39 cm ² ; Moderate to severe	≥ 0.4 cm ²
Regurgitant volume	< 30 mL/beat	30-44 mL/beat; Mild to moderate 45-59 mL/beat; Moderate to severe	≥ 60 mL/beat
Regurgitant fraction	< 30%	30%-39%; Mild to moderate 40%-49%; Moderate to severe	≥ 50%

MR: mitral regurgitation; MV: mitral valve; LA: left atrium; LV: left ventricle; TVI: time velocity integral. *At Nyquist limit between 50-70 cm/s. Color Doppler gain needs to be optimized

ASSESSMENT OF SEVERITY OF MR

Doppler echocardiography is the primary method for the detection and quantification of MR [Table 3]^[16]. The density of the continuous wave Doppler signal of the MR envelop is a useful qualitative parameter of MR severity. In general, small, faint MR jets with little or no flow convergence zone indicate mild MR, while large and dense jets with a large flow convergence or vena contracta are typically severe. A comprehensive color and spectral Doppler evaluation of MR using semi-quantitative and quantitative parameters should be performed when more than mild MR is suspected^[17].

An accurate assessment of MR severity is crucial for appropriate management and patient selection for interventional procedures. Given the limitations of standard echocardiographic methods in quantifying severe secondary MR, the concept of functional MR proportionality to the LV size has been proposed to accurately identify patients with clinically significant secondary MR^[18]. If the regurgitant volumes of severe functional MR is still proportional to the LV size, the patient is less likely to benefit from MV interventions. On the other hand, when the regurgitant volumes become disproportional to the degree of LV dilation (MR is greater than expected for the given LV size), the patient is more likely to benefit from MV interventions^[18]. This concept has gained more interest after the recent controversy about the results of the COAPT (Transcatheter Mitral-Valve Repair in Patients with Heart Failure) and MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) trials^[19,20]. In these two large randomized trials on MitraClip placement for severe secondary MR, different echocardiographic eligibility criteria and definitions were used for MR severity^[21]. The COAPT trial included patients with an effective regurgitant orifice area (EROA) of at least 0.3 cm² and regurgitant volume (RVol) > 45 mL/beat, while MITRA-FR included patients with less severe functional MR, EROA of at least 0.2 cm² and RVol > 30 mL/beat. In addition, the COAPT trial included only patients with LV end-systolic dimension of 70 mm or less, while MITRA-FR did not have restrictions regarding LV size. Given the conflicting results of these two trials, further studies to test the concept of disproportionate functional MR are needed. Meanwhile, careful patient selection for MitraClip is essential to achieve favorable outcomes.

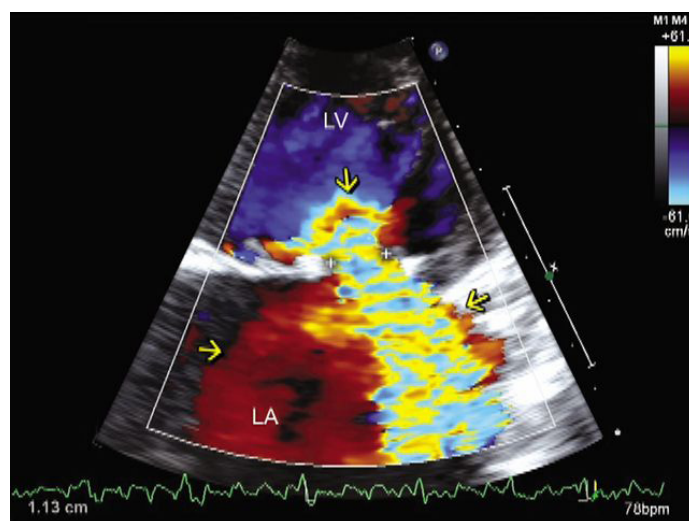


Figure 8. Two-dimensional transthoracic echocardiography in apical four-chamber view in a patient with severe MR. The vertical arrow points to a large flow acceleration, and the distance between the two + signs represents the vena contracta width, which measures 1.13 cm, indicative of severe MR. Not only the turbulent flow signals (right arrow in LA) but also the accompanying laminar flow signals (red, left arrow in LA) moving in the same phase as the turbulent flow signals represent MR. Thus, MR flow signals practically completely fill the LA, indicative of torrential MR. MR severity would have been underestimated if the red laminar signals were not taken into account. LV: left ventricle; LA: left atrium; MR: mitral regurgitation. Reproduced with permission from Manjunath *et al.*^[4]

COLOR DOPPLER

Color flow Doppler (CD) is commonly used for the detection and assessment of MR severity^[22]. This technique allows visualization of MR and identifies several characteristics of the regurgitant jet including number of jets, site, direction and the three components of the regurgitant jet (flow convergence, vena contracta and jet area)^[1,4]. Obtaining CD imaging of the MV in the parasternal short-axis view is important to localize the site of the MR jet. The spatial orientation of the regurgitant jet area within the LA during ventricular systole is proportional to the severity of MR^[23]. On the basis of the percentage ratio of the color jet area to the LA, MR can be graded as mild, moderate or severe if the ratio is < 20%, 20%-40% or > 40%, respectively^[23]. However, it is important to understand that there are several technical and hemodynamic factors that can influence the relationship between the jet size and MR severity. For instance, using inappropriate Nyquist limit or color gain could over- or underestimate the color jet size. A lower Nyquist limit will exaggerate lower velocities, and thus make the MR jet appear larger, while reducing the color gain results in a smaller jet and vice versa^{[Figure 9]^[4]}. Thus, it is recommended to use a standard Nyquist limit between 50-70 cm/s and optimize color gain to eliminate random lower flow velocity signals or color artifacts in the LA^[1]. CD could be misleading in acute MR and in patients with hypotension or tachycardia. On the other hand, MR jet may appear larger in patients with elevated LV end-diastolic pressure due to high driving pressure across the MV, which can be seen in cases of significant aortic stenosis, LV outflow obstruction or uncontrolled hypertension. CD could also overestimate MR jet area when multiple jets are present^[24].

Eccentric MR jets are sometimes difficult to detect and appear smaller due to loss of energy when the regurgitant jet impinges the LA walls or the other leaflet, known as Coanda effect^{[Figure 10]^[4,25]}. This problem is often obviated when one takes into account the laminar (red/blue) flow signals moving in the same phase as the turbulent (mosaic colored) eccentric jet. Loss of energy from impingement results in low velocity and therefore laminar MR signals. Presence of eccentric jet generally indicates significant MR and should raise the suspicion of the possibility of underlying structural abnormalities such as torn chord or leaflet perforation. Careful evaluation of other echocardiographic parameters such as the presence of large

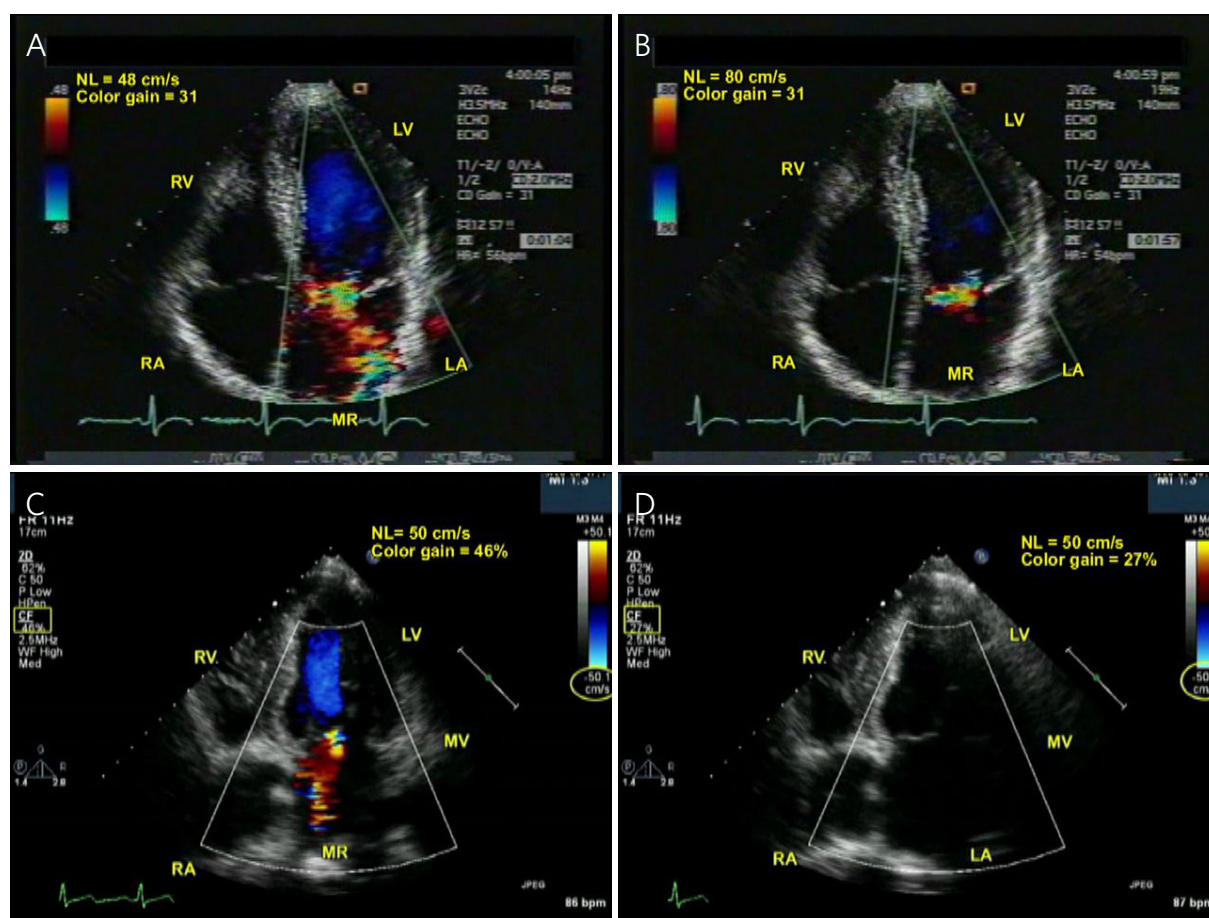


Figure 9. Two-dimensional transthoracic echocardiography. Apical four-chamber views. A, B: when the NL of 48 cm/s (A) was increased to 80 cm/s (B) without moving the transducer and keeping the color Doppler gain constant at 31, the MR flow signals showed marked reduction in size in this patient with substantial MR; C, D: in another patient with substantial MR, reducing color Doppler gain from 46% (C) to 27% (D) keeping the NL constant at 50 cm/s and not moving the transducer resulted in complete disappearance of MR signals. Color gain is optimized by first increasing it till stationary artifactual echoes often extending beyond the LA walls appear and then decreasing it gradually till they just disappear. LA: left atrium; MR: mitral regurgitation; NL: Nyquist limit; RV: right ventricle; RA: right atrium; LV: left ventricle; MV: mitral valve. Reproduced with permission from Manjunath *et al.*^[4]

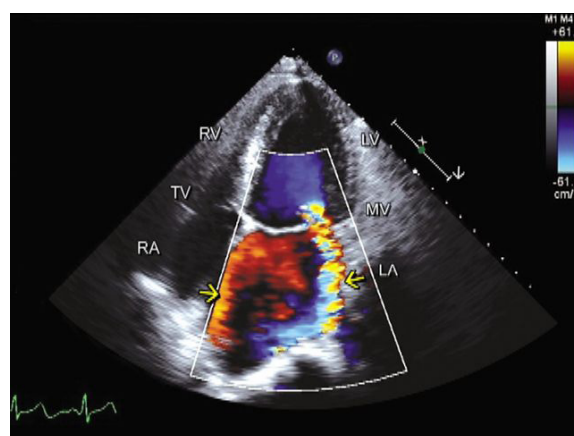


Figure 10. Two-dimensional transthoracic echocardiography in apical four-chamber view in a patient with severe MR. A relatively small size wall hugging turbulent eccentric MR jet (right arrow) consistent with mild MR is noted. If the laminar flow signals (red, left arrow) moving in the same phasic manner as the turbulent MR jet (to differentiate them from pulmonary venous inflow) are taken into account, MR severity would not be underestimated and would be correctly considered severe, as the combined turbulent and laminar flow signals virtually fill the whole LA. The laminar low velocity red flow signals also representing MR result from the high velocity turbulent flow signals striking the LA lateral wall resulting in marked reduction of their velocity. RV: right ventricle; RA: right atrium; LV: left ventricle; LA: left atrium; MV: mitral valve; MR: mitral regurgitation; TV: tricuspid valve. Reproduced with permission from Manjunath *et al.*^[4]

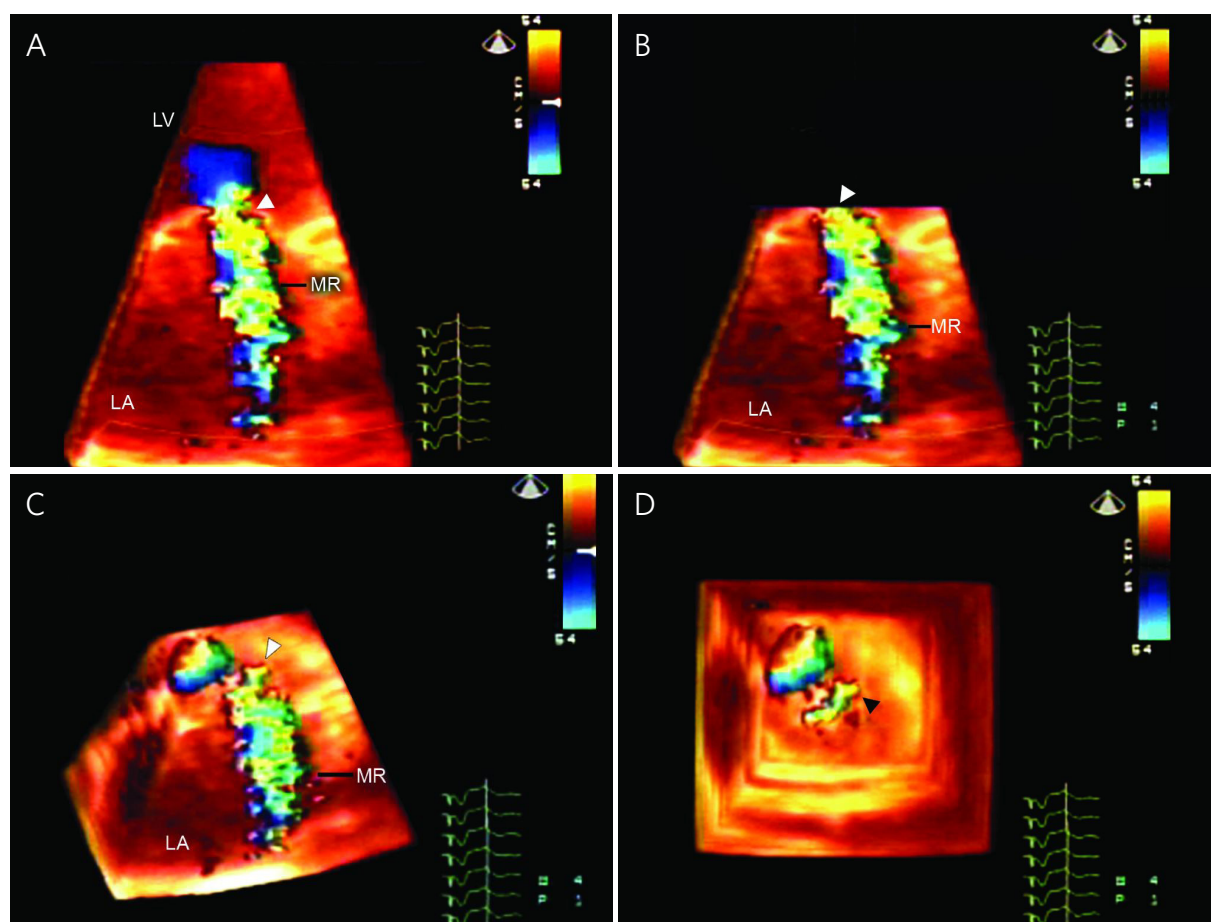


Figure 11. A-D: Live/real-time three-dimensional color Doppler transthoracic echocardiographic technique for assessment of vena contracta area. Three-dimensional color Doppler dataset showing MR (A) cropped from top to the level of the vena contracta (arrowhead, B) and tilted to view it en face (arrowheads in C and D). The vena contracta area is then measured by planimetry. MR: mitral regurgitation. Reproduced with permission from Khanna *et al.*^[30]

convergence zone, elevated mitral inflow E velocity (> 1.2 m/s) or systolic flow reversal into pulmonary veins are also useful for accurate assessment of MR severity in such cases of eccentric MR.

Due to several technical and hemodynamic limitations, CD should not be used alone to assess MR severity^[22]. Therefore, an integrative approach using supportive spectral Doppler and 2D echocardiographic parameters is recommended when suspecting significant MR on CD. The utility of 3D CD in assessing MR severity is emerging because of its ability to view both the flow convergence zone and the vena contracta en face^[26].

VENA CONTRACTA

The vena contracta width is the narrowest region of the MR jet that occurs at or immediately downstream of the regurgitant orifice. When assessed in 3D en face view, it represents the defect through which MR occurs or in other words the cross-sectional area of the effective regurgitant orifice area [Figures 11 and 12]^[27]. For accurate measurement, VC in 2D imaging should be assessed in a zoom view perpendicular to the commissural line (e.g., the parasternal long axis or the apical 4-chamber view). In general, the VC is independent of flow rate or driving pressure^[28]. Regardless of MR etiology, VC is a useful semi-quantitative measure of MR severity in both central and eccentric jets^[27]. It is recommended to average VC measurements over 2 to 3 beats using two orthogonal planes^[22]. A VC width of < 3 mm indicates mild

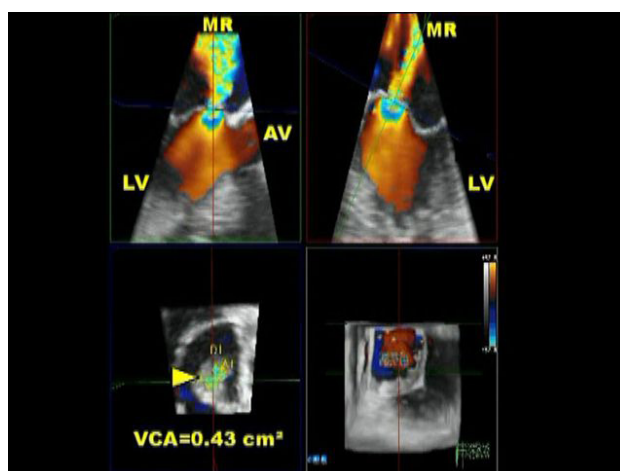


Figure 12. Live/real-time three-dimensional color Doppler transesophageal echocardiographic technique for assessment of VCA. The three-dimensional dataset is cropped at the level of the MR vena contracta (MR jet origin) and cropped to view it en face (arrowhead). VCA measured 0.43 cm², indicative of severe MR. VCA: vena contracta area; LV: left ventricle; MR: mitral regurgitation; AV: aortic valve. Copyright with Navin C. Nanda

MR, whereas a width of > 7 mm defines severe MR^[22]. If multiple jets are noted, the widths of VC maybe additive. However, VC may underestimate MR severity in cases of multiple jets or if there is an elliptical regurgitant orifice. On the other hand, VC could overestimate MR severity if regurgitant jet is limited to early, mid or late systole^[29]. Recently, emerging data show that 3D area measurements of VC as well as flow convergence may provide useful quantitative assessment of MR severity^[30,31].

FLOW CONVERGENCE/PROXIMAL ISOVELOCITY SURFACE AREA

Imaging the flow convergence region proximal to the regurgitant orifice is highly recommended for MR quantitation. Qualitatively, the presence of a large convergence zone indicates substantial MR [Figure 8]. Quantitatively, the flow convergence method can be used to quantify the regurgitant flow rate, which is used to calculate the EROA, RVol and regurgitant fraction (RF)^[32]. These are essential measures of lesion severity, volume overload and predict outcomes for patients with severe MR. The proximal isovelocity surface area (PISA) method is based on the continuity principle^[33]. In any regurgitant lesion, blood flow accelerates towards the regurgitant orifice and creates concentric hemispherical isovelocity surfaces (shells) centered at the regurgitant orifice [Figure 13]^[34]. The blood flow rate across all these hemispherical surfaces is constant and equal to the flow rate through the regurgitant orifice^[33]. Color flow mapping provides the ability to visualize any one of these hemispheres that corresponds to certain aliasing velocity threshold. The apical 4-chamber view is recommended for optimal PISA measurements. The area of interest is optimized by lowering the image depth and shifting the Nyquist limit towards the direction of MR jet, i.e., down on TTE and up on TEE. To calculate the flow rate, multiply the aliasing velocity (Va) by $2\pi r^2$ (area of corresponding hemisphere), where r is PISA radius [Figure 14]^[4]. On the basis of regurgitant flow, EROA, RVol and RF can be calculated using standard formulas.

$$\text{Regurgitant flow} = V_a \times 2\pi r^2$$

$$\text{EROA} = \text{Regurgitant flow} / \text{Peak velocity of MR}$$

$$\text{RVol} = \text{EROA} \times \text{Velocity Time Interval of MR}$$

$$\text{RF} = \text{RVol} / \text{stroke volume of regurgitant valve}$$

A simplified method to calculate EROA is to measure PISA radius at Nyquist limit of 40 cm/s, assume peak MR jet velocity of 5 m/s, and then $\text{EROA} = r^2/2$ ^[17]. Regardless of MR etiology, EROA of $\geq 0.4 \text{ cm}^2$ and/or RVol

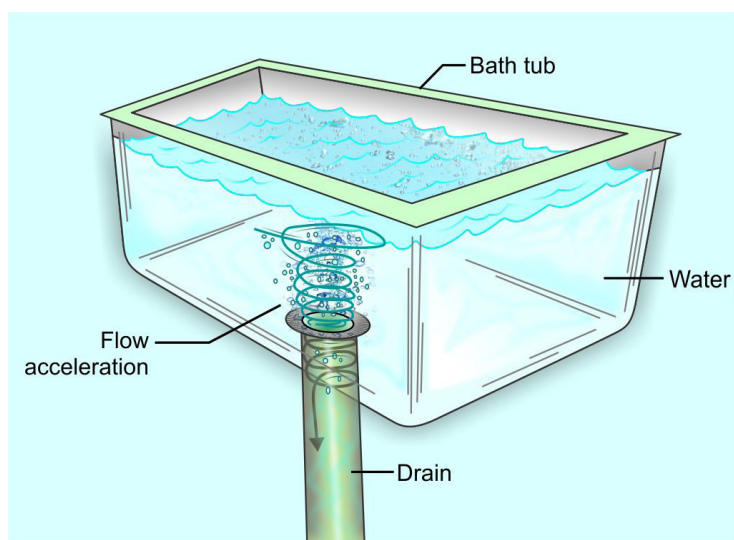


Figure 13. A simple example of the generation of flow acceleration can be shown by observing the draining of water from a household bathtub. Flow acceleration or a localized area of high velocity develops as the large body of water moves toward the “hole” or opening in the bottom of the tub, through which water flows into the drain. Adjacent to this “hole,” the area of flow acceleration becomes smaller and tends to take the shape and size of the circular “hole” (vena contracta). Reproduced with permission from Kapur *et al.*^[34]

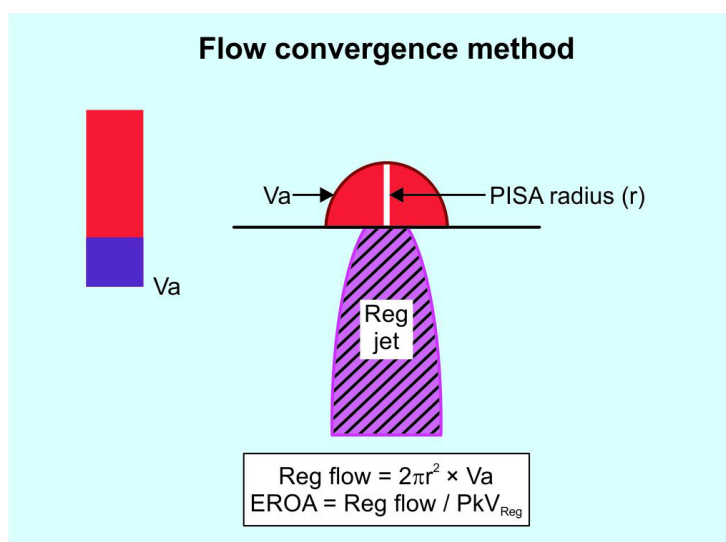


Figure 14. Schematic depiction of the flow convergence or PISA method for quantitating valvular regurgitation. V_a is the velocity at which aliasing occurs in the flow convergence toward the regurgitant orifice. PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; PkV_{Reg} : peak velocity of the regurgitant jet determined by continuous wave Doppler; Reg flow: regurgitant flow; Reg jet: regurgitation jet. Reproduced with permission from Manjunath *et al.*^[4]

≥ 60 mL indicates severe MR [Table 2]. However, in secondary MR, $EROA \geq 0.2 \text{ cm}^2$ and/or $RVol \geq 30 \text{ mL}$ is associated with worse outcomes^[35].

Similar to VC measurement, the PISA method could be misleading if multiple jets or noncircular regurgitant orifices present. It could be technically challenging to obtain accurate PISA measurements in cases of eccentric jets. A major problem in quantifying MR severity by the PISA method is the assumption that the flow convergence is hemispherical in shape, which is not the case in most patients with MR. Thus, EROA by PISA equation is not recommended in the presence of MV devices including MitraClip, because

the assumption of hemispherical proximal flow conversion zone is even further disrupted by the device^[1,14]. The use of 3D echocardiography could help overcome some of these limitations.

SPECTRAL DOPPLER

Spectral Doppler remains useful and provides important parameters for quantitative assessment of MR severity [Table 3]. Both the mitral to aortic TVI ratio of > 1.4 and the systolic flow reversal into pulmonary veins are specific signs of severe MR. Similar to the quantitative volumetric method, the pulsed wave Doppler method is time-consuming and has several limitations^[36].

ROLE OF STRESS TESTING

Both in primary and secondary MR, exercise stress echocardiography can provide additional diagnostic and prognostic information in asymptomatic patients^[37]. For patients with severe MR and equivocal symptoms, exercise testing can be useful in assessing symptomatic status and functional capacity. Inadequate increase in LV ejection fraction with exercise predicts worse postoperative LV function^[38]. In secondary MR, an increase in EROA $> 0.13 \text{ cm}^2$ during exercise is associated with worse cardiovascular outcomes^[37]. Currently, there is no role for pharmacological stress echocardiography in evaluation of MR severity.

CONCLUSION

2D echo imaging is the modality of choice for evaluating the etiology and mechanism of MR and associated lesions. MR severity in real world practice is semi-quantitatively assessed by eyeballing the proportion of the LA area occupied by the regurgitant jet on 2D/color Doppler imaging. This is supplemented by linear measurements of flow convergence and VC. When MR appears moderately severe or severe by these methods and intervention, where MitraClip is a consideration, more comprehensive and complicated quantitative echo methods, which may include 3D imaging, are used.

DECLARATIONS

Authors' contributions

Read and approved the manuscript: Smer A, Nanda NC, Akdogan RE, Elmarzouky ZM, Dulal S

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Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Percutaneous mitral valve repair in acute mitral regurgitation: case report and review of the literature

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Abstract

Acute mitral regurgitation is a heterogeneous and life-threatening pathology, with severe hemodynamic consequences and extremely adverse outcomes. Traditionally, the definitive treatment is prompt surgical intervention after hemodynamic stabilization. Nowadays, however, percutaneous repair of mitral valve with MitraClip device has emerged as a safe and effective therapeutic option. Evidences in this field are still scarce. Hereby, we report the case of an 82-year-old woman with lateral ST-elevation myocardial infarction determining severe acute mitral regurgitation (MR) with an asymmetric leaflet tethering mechanism. Due to prohibitive operative risk and unstable hemodynamic status, the patient underwent a successful urgent MitraClip procedure with optimal reduction of MR and immediate hemodynamic improvement. Moreover, we provide a review of the available literature regarding the echocardiographic assessment of acute MR, results of published cases and possible management of this complex pathology.

Keywords: MitraClip, edge-to-edge, percutaneous mitral valve repair, acute mitral regurgitation, acute myocardial infarction, cardiogenic shock, papillary muscle rupture



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INTRODUCTION

Percutaneous repair of mitral regurgitation (MR) with the MitraClip device (Abbott Vascular, Abbott Park, Illinois, USA) is an established therapeutic option for patients with prohibitive surgical risk and anatomically suitable mitral valve (MV)^[1]. Implanted in over 100,000 patients worldwide, MitraClip procedure is safe and boasts a highly favourable risk-benefit ratio. While the impact of percutaneous MV repair on outcomes in chronic severe symptomatic MR has been evaluated for years in detail, data regarding the use of percutaneous edge-to-edge procedure in patients with severe acute MR are scarce and limited to case reports or small-size registries. Acute MR is a complex and heterogeneous pathology, with severe hemodynamic consequences and extremely adverse outcomes^[2]. Traditionally, in most cases, after hemodynamic stabilization, the definitive treatment is surgical intervention. Nowadays, the MitraClip device is proving to be a valuable therapeutic option in high-risk patients.

Hereby, we present a case of acute severe ischemic mitral regurgitation successfully treated with MitraClip procedure.

CASE DESCRIPTION

We report the case of an 82-year-old female patient, who presented to emergency department for chest pain lasting for 72 h. The EKG revealed a latecomer lateral ST-elevation myocardial infarction, with ST-depression in V1-V4, ST-elevation and q waves in V7-V9. She had a history of arterial hypertension, rheumatoid arthritis, thalassemia minor, and radiotherapy-treated tongue cancer.

A bedside echocardiogram showed a left ventricular ejection fraction (LVEF) of 40% due to akinesia of posterior and lateral walls, normal left ventricular and atrial dimensions, mild MR, normal right ventricular function and size. Urgent coronary angiography was performed and showed a flow-limiting stenosis in the proximal tract of a dominant circumflex coronary artery. The coronary lesion was treated with balloon angioplasty and implantation of two drug-eluting stents. A severe no-reflow followed and prompted the use of intraortic balloon pump (IABP) for hemodynamic stabilization and the intracoronary injection of nitroprusside and adrenaline. The patient was transferred to Coronary Care Unit and remained hemodynamically stable for the subsequent 24 h.

Then, a sudden hemodynamic collapse occurred, with pulmonary congestion and hypotension requiring intubation and high-dose vasopressors. Trans-thoracic and trans-esophageal echocardiogram (TEE) showed acute severe MR with eccentric jet directed towards the posterior wall of left atrium, due to extreme tethering of the posterior leaflet with partial posteromedial papillary muscle rupture and pseudoprolapse of the anterior leaflet [Figure 1]. The patient was deemed inoperable due to prohibitive surgical risk (age, subacute myocardial infarction with no-reflow injury, upper thorax radiotherapy, dual antiplatelet therapy, hemodynamic instability; STS score - risk of mortality: 66.6%; Euroscore II: 43.52%) and despite the highly challenging morphology of valvular disease, a salvage MitraClip procedure was the only feasible path. The mechanism of MR was complex: a Carpentier type IIIC (asymmetric systolic restriction) with a main jet located at A3-P3 extended to the medial section of A2-P2, plus a partial posteromedial papillary muscle rupture implicating an additional risk of mechanical complications, a coaptation gap > 10 mm, a posterior leaflet of 9 mm, but without calcifications at the grasping zone and with a suitable MV area (> 4 cm²)^[3].

The patient underwent an urgent percutaneous edge-to-edge procedure under general anaesthesia, with IABP and vasopressor support, and using fluoroscopic and TEE guidance. An XTR Clip was first implanted in A3-P3 position with residual moderate MR and mean gradients of 3 mmHg [Figure 2], then an NTR Clip was used in A2-P2 position with a resulting minimal MR and mean gradients of 4 mmHg [Figure 3].

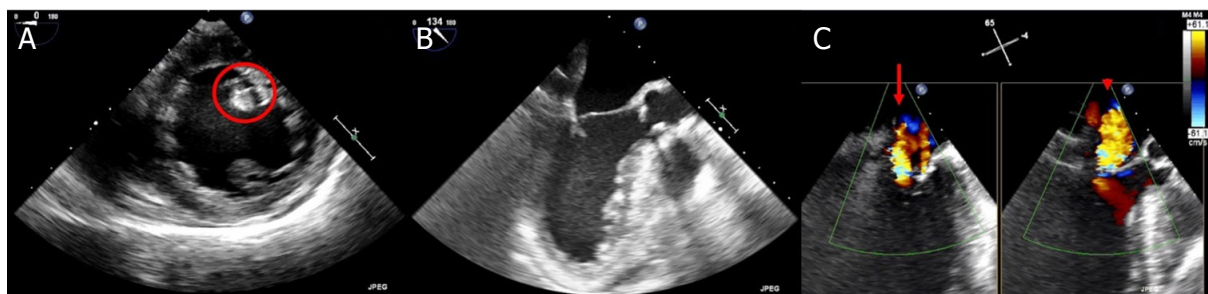


Figure 1. Baseline trans-esophageal echocardiogram showing partial postero-medial papillary muscle rupture (A, circle), extreme tethering of posterior leaflet with pseudoprolapse of anterior leaflet (B) and wide eccentric jet of severe mitral regurgitation mainly originating from A3-P3 (C, arrow) and extended to the medial section of A2-P2 (C, arrowhead)

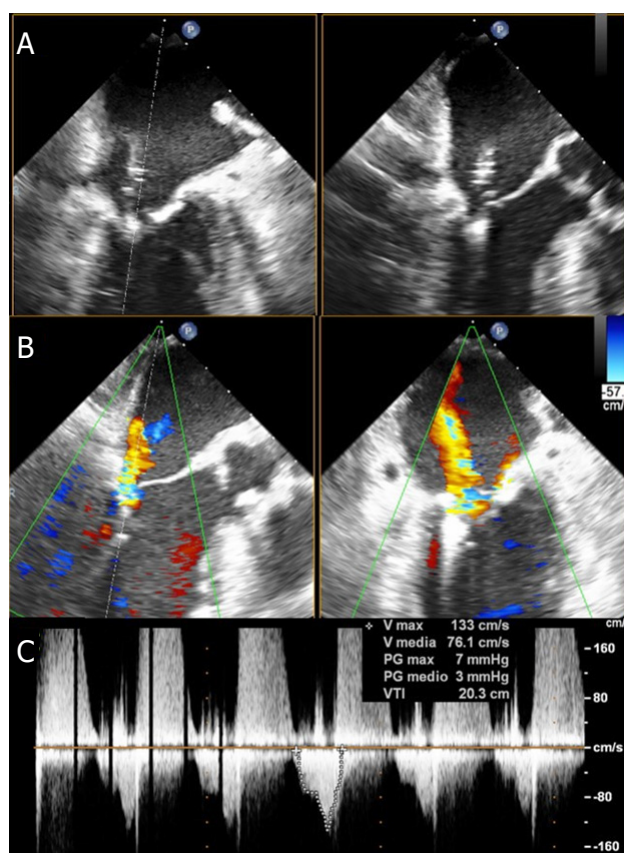


Figure 2. Intraprocedural trans-esophageal echocardiogram of XTR clip implantation: A3-P3 grasping (A), residual moderate mitral regurgitation located laterally to the clip (B) and transmitral gradients (C)

The patient's hemodynamics progressively improved, and she was successfully weaned off mechanical ventilation and pharmacological support. Her post-operative recovery was uncomplicated and the patient was discharged on the tenth post-procedural day with residual mild MR and mean gradients of 5 mmHg [Figure 4].

DISCUSSION

Acute MR is a medical and surgical emergency. Indeed, differently from chronic valvular diseases, acute MR occurs suddenly in normal sized hearts, without time for adaptative left atrial and ventricular enlargement. This results in a rapid increase of left atrial pressure with consequent pulmonary congestion

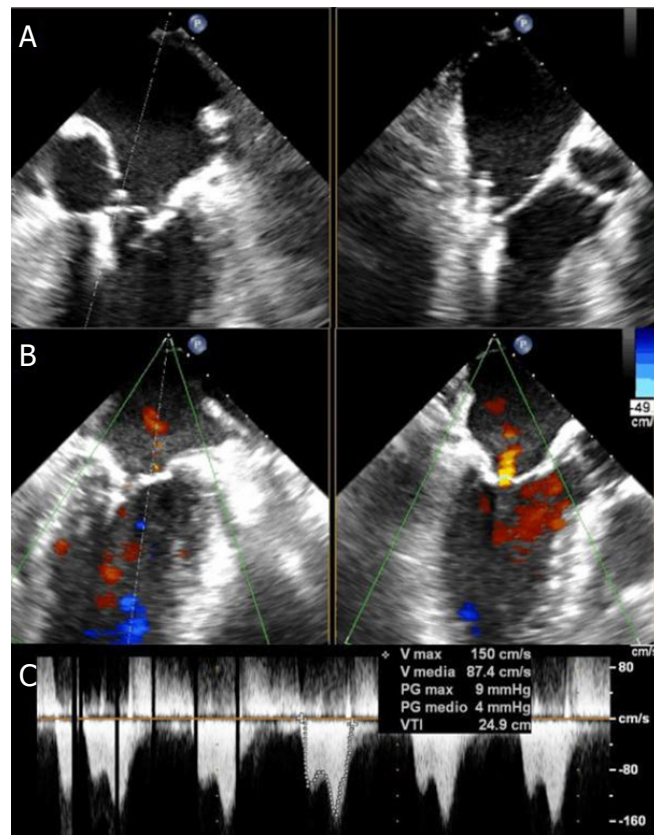


Figure 3. Intraprocedural trans-esophageal echocardiogram of NTR clip implantation: A2-P2 grasping (A), residual minimal mitral regurgitation (B) and transmitral gradients (C)

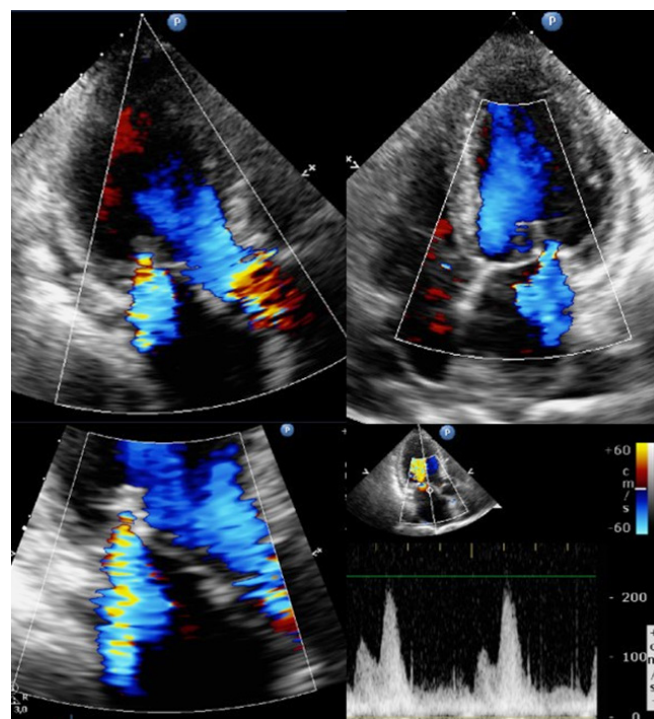


Figure 4. Discharge trans-thoracic echocardiogram showing residual mild mitral regurgitation and mean gradient of 5 mmHg

Table 1. Classification of acute mitral regurgitation mechanisms and causes

Mechanism	Cause
Organic/structural damage	
Carpentier type I (normal leaflet motion): perforation	Infective endocarditis Device-related
Carpentier type II (excessive leaflet motion): prolapse/flail (papillary muscle rupture, chordal rupture)	Infective endocarditis Myocardial ischemia Myxomatous degeneration Fibroelastic deficiency Idiopathic chordal rupture Device-related
Functional alteration	
Carpentier type III (restricted leaflet motion): symmetric/asymmetric systolic restriction	Myocardial ischemia
Carpentier type IV: systolic anterior motion of the leaflets	Hypertrophic cardiomyopathy Takotsubo cardiomyopathy

"Carpentier types" refer to expanded Carpentier classification^[3]

and, despite initial hyperdynamic ventricular contraction, a risk of progressive reduction of cardiac output with hypotension and peripheral hypoperfusion^[4]. Thus, patients with acute MR usually present with severe dyspnea, and slip towards cardiogenic shock.

Timely diagnosis may be insidious, due to nonspecific clinical pattern and equalization of left ventricular and atrial pressures leading to a soft or absent murmur^[2]. Even pulmonary edema can be atypical with unilateral involvement if the regurgitant jet is eccentrically directed into either the right or the left pulmonary veins^[2]. Echocardiography is key to diagnosis and proper management of the different causes of this disease^[5].

Traditional management involves medical stabilization and surgical intervention, with a timing strictly related to the specific etiology of valve dysfunction^[6]. MitraClip device has emerged as a new therapeutic alternative which is promising and potentially life-saving.

In the following sections, the main aspects of acute MR will be analysed with a focus on the amenability and use of percutaneous edge-to-edge repair technique in this condition.

Etiology

Identifying the precise mechanism and cause of acute MV disease is fundamental to tailor the most appropriate therapeutic strategy for each patient. Acute MR counts few mechanisms and many possible causes, as detailed in Table 1. First of all, the distinction between structural damages and functional alterations is fundamental, because organic causes always require repair, whereas functional causes may improve after targeting the underlying myocardial infarction, ischemia, or systolic dysfunction^[5].

One major organic cause is chordal rupture which may occur in an otherwise totally normal valve or in a MV affected by Barlow's disease or fibroelastic deficiency.

Device-related MR is a rare yet possible complication of left ventricular mechanical support devices due to catheter impingement in the chordal apparatus or leaflet tissue^[7]. Iatrogenic MR is also reported after percutaneous mitral valvotomy for rheumatic mitral stenosis, albeit unlikely if patients are adequately selected.

Infective endocarditis can cause leaflet perforation and tears, papillary muscle and chordal rupture or may reduce systolic coaptation due to masses or abscesses interfering with leaflets' apposition.

Extremely rare etiologies include chest traumas, systemic inflammatory diseases or acute rheumatic fever which remains a serious concern in endemic areas^[8,9].

Ischemic papillary muscle rupture is another major cause of acute massive MR, with more frequent involvement of the posterior papillary muscle during inferior myocardial infarctions.

Acute myocardial ischemia or infarction may cause acute functional MR with systolic symmetrical or asymmetrical leaflet tethering, due to global or regional ventricular systolic dysfunction.

Another functional cause of MR is systolic anterior motion (SAM) of mitral leaflets in hypertrophic obstructive cardiomyopathy or Takotsubo cardiomyopathy^[2].

Echocardiography

Diagnosis of acute MR

Echocardiography is essential for diagnosis. As opposed to chronic MR, left atrial and ventricular sizes are usually normal in acute MR, except for preexisting conditions influencing chambers' dimension, compliance and hemodynamic tolerance. For instance, patients with a history of chronic MR and preserved ventricular systolic function have enlarged cardiac volumes and tolerate the further volumetric increase better than patients with normal sized hearts or with preexisting reduced LVEF. Color Doppler may underestimate the severity of MR, owing either to rapid equalization of left atrial and ventricular pressures or to an eccentric direction of the regurgitant jet with "Coanda" effect. Consequently, the use of color Doppler-based quantitative measures such as regurgitant volume and effective regurgitant orifice area may be misleading and even challenging, due to severe acute congestive heart failure with tachycardia. Vena contracta width and continuous wave Doppler signal represent reliable semiquantitative tools to quickly evaluate the significance of MR. A triangular and dense continuous wave Doppler curve supports the diagnosis of acute MR. It mirrors the rapid decline in late systolic velocity as a consequence of the abrupt increase in left atrial pressure. Systolic pulmonary venous flow reversal in one or both pulmonary veins can be found but tachycardia or atrial fibrillation can mask these findings. Any measure or value should be interpreted in the clinical context, as patients with acute heart failure and acute MR may appear to have only moderate MR when assessed by semi-quantitative and quantitative methods. Indeed, an acute significant MR should be suspected in patients with a clinical pattern of acute heart failure, with evidence of hyperdynamic LV without systolic or diastolic dysfunction, and with anatomic imaging of MV lesions^[10,11].

Trans-thoracic echocardiography is the first-line examination in the assessment of acute dyspnea, feasible at bedside and sufficient to raise the clinical suspicion, but often inconclusive regarding the identification of the mechanism of MR, the evaluation of the MV anatomy and preoperative planning, which all require TEE. As such, three-dimensional (3D) echocardiography should always be adopted, as it provides anatomical details not detectable with two-dimensional (2D) imaging, enabling a dynamic and comprehensive assessment of MV tissue, and seizes dataset for off-line multiplanar reconstructions^[12].

Mechanism and cause of MR

The first step of echocardiographic evaluation of MR mechanism is the distinction between organic/structural damage and functional alteration of MV [Table 1]. Close assessment of leaflet motion, anatomic lesions and finally the Color Doppler-based evaluation of convergence area and regurgitant jets are required.

A structural lesion with normal leaflet motion is generally due to a leaflet perforation. In this case, TEE should evaluate the position, shape and dimensions of the perforation, detect any sign suggestive of endocarditis, such as masses, vegetations or abscesses and explore mitral-aortic junction, left ventricular

outflow tract and the position of other intracardiac devices. Indeed, an ambitious combined percutaneous procedure of MitraClip plus occluder would be contraindicated in the presence of active endocarditis, and an accurate preoperative planning should take into account the risk of iatrogenic obstruction of ventricular outflow or interference with proximally-located prostheses^[13].

Leaflet flails and prolapse are categorised as Carpentier type II mechanism and occur through sudden rupture of chordae tendineae or papillary muscles due to many possible causes^[11]. Myxoid degeneration or Barlow's disease is a major cause of chordal rupture and remains extremely challenging for percutaneous repair due to altered anatomy, including extensive leaflet thickening, multi-segmental prolapse, elongated or fused chordae tendineae, diffuse calcifications and annular dilatation^[14]. Beyond procedural challenges, the main issue is the balance between a relevant residual MR due to the highly mobile and redundant leaflets and a resultant iatrogenic mitral stenosis owing to extensive grasping with multiple clips. However, the introduction of MitraClip XTR device, with a wider reach and longer clip arms than NTR, has broadened the "graspable" MV anatomies, including Barlow's disease, as documented by a few case series^[15-17]. Nonetheless, myxoid degeneration appears early in life and patients are usually referred for surgery due to young age and low risk, on the contrary fibroelastic deficiency affects elderly people with significantly different operative risk. In fibroelastic deficiency MV is characterized by impaired production of connective tissue and shows thin leaflets, prolapse of single segments, and rupture of thin chordae with limited flail width^[14]. MitraClip has been shown to be feasible and safe in this type of MV anatomy, even in octogenarians, but care should be taken in cases of fragile leaflet tissue due to the risk of grasping-related leaflet tears or lacerations^[18].

Papillary muscle rupture is a severe, albeit rare, mechanical complication of acute myocardial infarction. This anatomic lesion is challenging given the large flail width and flail gap with frequent commissural localization requiring an extensive grasping with a concomitant high risk of chordal entanglement^[19]. As a papillary muscle head may mimic an endocarditic mass, clinical context should guide the differential diagnosis^[20]. Moreover, infective endocarditis itself may be causative of chordal rupture and papillary muscle laceration, in the presence of typical echocardiographic criteria such as vegetations and abscesses^[21].

Among functional alterations of MV, the main cause of acute MR is myocardial ischemia. Indeed, in the very acute phase of myocardial infarction, even modest valve tenting due to regional and/or global left ventricular dysfunction may result in hemodynamically-significant MR^[22]. Echocardiography should be performed to assess the presence of wall motion abnormalities and myocardial scarring, and the "symmetry" of mitral leaflets with respect to their point of coaptation. In cases of asymmetric tenting, it is generally the posterior leaflet that tethers while the anterior leaflet shows a "pseudoprolapse" motion. The MR jet is eccentric and oriented against the posterior wall of left atrium. In cases of symmetric tethering, both leaflets are tented but the coaptation point is displaced apically at the leaflets' tips, and the jet is typically central^[23].

An infrequent cause of acute MR is SAM of mitral leaflet, which represents a life-threatening condition and may result also in critical left ventricular outflow tract obstruction. Hypertrophic obstructive cardiomyopathy is the main pathology associated with SAM and is characterized by abnormalities of MV and subvalvular apparatus, such as malpositioned papillary muscles, elongated chordae and thickened leaflets^[24]. These anatomic features may impact on transmitral gradients and residual MV area after MitraClip procedure^[25]. SAM with left ventricular outflow obstruction may occur in several other conditions such as Takotsubo cardiomyopathy, hypertensive hypertrophic cardiopathy, hypovolemia, severe bleeding, sepsis, vasodilatation, sympathetic activation, pericardial tamponade, after aortic valve replacement, and after surgical mitral valve repair^[25]. In these acute conditions a transcatheter edge-to-edge technique certainly sounds appealing to target both MR and hypotension.

Finally, rheumatic heart disease is commonly regarded as a contraindication to MitraClip procedures, owing to high risk of mitral stenosis. However, a recently published case report has shown the feasibility of percutaneous MV repair in a rheumatic MV with baseline mean gradients inferior to 4 mmHg^[26]. Accurate measurement of MV area through 3D-based multiplanar reconstruction, evaluation of trans-mitral mean gradients and exclusion of calcifications at the grasping area are essential to decision-making and preoperative planning.

As outlined above, absolute anatomic limitations are very few. Hahn^[27] listed the echocardiographic features associated with ideal and challenging anatomies and highlighted a few relative contraindications. The absolute contraindications include severe and extended calcifications of the grasping zone, short leaflet length (< 7 mm) and small baseline MV area (< 3.5 cm²)^[15].

Real-world evidences of MitraClip procedure in acute MR

Real-world experience on percutaneous edge-to-edge repair of acute MR is uniquely derived from case reports and small-size registries, listed and synthesized in Table 2^[19,28-43].

The vast majority of cases occurred as complications of acute myocardial infarction, due to either ischemic leaflet tethering or papillary muscle ruptures (more often the posteromedial one). A primary PCI was always performed, except for late presentations due to the likely risk of reperfusion injury of already necrotic walls. The hemodynamic status was generally critical with evidence of cardiogenic shock and pulmonary edema requiring intubation, inotropes and mechanical support, mainly IABP and only in few cases veno-arterial extracorporeal membrane oxygenation. The Heart Team's decision to proceed with MitraClip was primarily guided by the high surgical risk due to hemodynamic instability, acute/subacute ischemia, dual antiplatelet therapy, advanced age or comorbidities in a few cases, and the favourable risk-benefit balance of percutaneous edge-to-edge approach. Hemodynamic stabilization and likelihood of MR improvement with revascularization or medical therapy were the main determinants of the timing of procedure. One to three clips were deployed with an almost complete procedural success, due to significant reduction of MR, huge reduction of left atrial pressures and increase of cardiac output. Haberman *et al.*^[42] reported one case of posterior leaflet tear during a second clip implantation, followed by urgent MV surgery and lastly by patient death. Early outcomes were promising, with high survival rates, sustained reduction of MR grade and improved functional class. These results are even more reassuring if compared with surgical ones; in a multicentre surgical registry of 279 patients treated with emergency surgery for acute severe MR, due to myocardial infarction, acute endocarditis or degenerative MV disease, the 30-day mortality was 22.5% with worse survival rates in case of acute myocardial infarction, endocarditis, shock, coronary artery disease and systolic dysfunction^[44]. Despite the evidences seem extremely optimistic regarding outcomes of MitraClip in almost every acute setting, a publication bias has to be recognized, and the interventionalists' and imagers' experience should be considered during Heart Team decision-making. Certainly, MitraClip shows several advantages over surgery. Firstly, MitraClip is safe and does not preclude a delayed surgical procedure in case of failure, thus a "bridge" procedure may be always attempted without significant additional risks. Secondly, percutaneous procedures permit to avoid the cardiopulmonary bypass and the associated systemic inflammatory storm and myocardial oxidative stress. Furthermore, transcatheter procedures do not cause abnormal motion of the right ventricle or interventricular septum, which may impact on long-term LV performance^[43].

Decision-making and management

We propose a flow-chart that may be helpful for acute MR decision-making and management [Figure 5].

Once acute MR is diagnosed, the initial goal is hemodynamic stabilization through inotropes/vasopressors and temporary mechanical circulatory supports (IABP, Impella and extracorporeal membrane oxygenation)

Table 2. Case reports and registries of MitraClip in patients with acute MR

Title	Ref.	Cause and mechanism of acute MR	Patients	Hemodynamic setting	Procedure and acute result	Early outcomes	Discharge	Follow-up
Case reports								
Percutaneous mitral valve repair using the MitraClip in acute cardiogenic shock	Zuern et al. ^[29]	Acute cardiogenic shock and MOF in ischemic cardiomyopathy (2 previous anterior wall myocardial infarctions)	51-year-old male LVEF = 15% LVESD = 58 mm LVEDD = 67 mm BNP = 2786 ng/L	Cardiogenic shock and MOF IABP and inotropes LAP = 36 mmHg PAP = 75/44 mmHg CO = 3.0 L/min	1 clip (A2-P2) MR grade = 1-2+ PCWP = 29 mmHg PAP = 66/37 mmHg CO = 4.3 L/min	Device success	Alive (postop day 7) LVEF = 15% LVESD = 59 mm LVEDD = 68 mm sPAP = 32 mmHg BNP = 1,210 ng/L	3-month NYHA II MR grade = 1-2+ LVEF = 20% LVESD = 54 mm LVEDD = 63 mm sPAP = 34 mmHg BNP = 681 ng/L
Successful Percutaneous Mitral Valve Repair with the MitraClip System of Acute Mitral Regurgitation due to Papillary Muscle Rupture as Complication of Acute Myocardial Infarction	Blige et al. ^[30]	Posterolateral STEMI, successful primary PCI of proximal circumflex artery with loss of marginal branch Complete rupture of the anterolateral papillary muscle with A1-P1 flail and lateral jet	60-year-old female IABP LVEF = 45%	Pulmonary edema and cardiogenic shock sPAP = 65 mmHg	7 days after admission 1 clip (A1-P1) MR grade = 0	Minor hemorrhagic stroke 2 days after MitraClip	Alive (postop day 9)	30-day MR grade = 1+
MitraClip for Papillary Muscle Rupture in Patient With Cardiogenic Shock	Wolff et al. ^[31]	Latecomer lateral STEMI, with occlusion of large first obtuse marginal artery Complete rupture of anterolateral papillary muscle with flail of A2	68-year-old male LVEF = 25% Mild to moderate right ventricular dysfunction STS score = 64% EuroSCORE II = 75%	Cardiogenic shock and ventricular arrhythmias IABP and inotropes Mean LAP = 37 mmHg v-waves = 55 mmHg	2 clips (A2-P2) MR grade = 2+ v-wave = 30 mmHg	Device success	MR grade = 1-2+ LVEF = 30% LVEDD = 51 mm LVEF = 38% RV function = normal	3-month NYHA II MR grade = 1-2+ LVEF = 38% LVEDD = 62 mm LVESD = 50 mm
MitraClip Implantation After Acute Ischemic Papillary Muscle Rupture in a Patient With Prolonged Cardiogenic Shock	Bahlmann et al. ^[32]	Lateral NSTEMI Complete rupture of the posterior papillary muscle	77-year-old male Log Euroscore = 78%	Cardiogenic shock and pulmonary edema IABP and inotropes Mean LAP = 21 mmHg Mean PAP = 24 mmHg Stroke volume index = 38 mL/m ² CO = 6.8 L/min CI = 3.2 L/min/m ² CI = 2.2 L/min/m ²	3 clips MR grade = 0 Mean LAP = 22 mmHg Mean PAP = 26 mmHg	Device success	Alive (postop day 16)	-
Percutaneous Mitral Valve Repair With Mitraclip System in a Patient With Acute Mitral Regurgitation After Myocardial Infarction	Rodriguez-Santamarta et al. ^[33]	Inferolateral STEMI, successful primary PCI of proximal circumflex artery Ischemic asymmetric posterior leaflet tethering A2-P2 and A3-P3	76-year-old male STS score = 6.7% Log Euroscore = 29.1%	Pulmonary edema	2 clips (A2-P2; lateral to the first one) MR grade = 1+ MV MG < 5 mmHg	MR grade (4th day) = 1+	Alive NYHA I	NYHA I

Effective Percutaneous "Edge-to-Edge" Mitral Valve Repair With MitraClip in a Patient With Acute Post-MI Regurgitation Not Related to Papillary Muscle Rupture	Tarsia <i>et al.</i> [364]	Inferior STEMI, successful primary PCI of right coronary artery and marginal branch, complete revascularization of left anterior descending artery after 48 hours	65-year-old female Log Euroscore = 42%	Cardiogenic shock and pulmonary edema IABP and inotropes	1 clip (A2-P2) MR grade = 0	Device success No major complications	Alive (postop day 7)	6-month NYHA I MR grade = 0
Acute Mitral Regurgitation Secondary to Papillary Muscle Tear Is Transcatheter Edge-to-Edge Mitral Valve Repair a New Paradigm?	Valle <i>et al.</i> [365]	Inferior STEMI, successful primary PCI of saphenous vein graft to right coronary artery Partial tear of the posteromedial papillary muscle with flail of A2-A3	84-year-old male LVEF = mildly reduced	Cardiogenic shock and MOF Mean LAP = 29 mmHg v-wave = 59 mmHg	3 clips in a "zipper" approach MR grade = 1+ MV MG = 5 Mean LAP = 14 mmHg v-wave = 20 mmHg.	-	Alive	6-week NYHA II MR grade = 1-2+
Use of MitraClip for Postmyocardial Infarction Mitral Regurgitation Secondary to Papillary Muscle Dysfunction	Yasin <i>et al.</i> [366]	Inferior NSTEMI Partial rupture of posteromedial papillary muscle with flail of posterior leaflet	68-year-old male	Cardiogenic shock and pulmonary edema v-a ECMO	2 clips (A2-P2, P1-P2) MR grade = 1+	MR grade (3 rd day) = 1+ Device success	Alive	30-day MR grade = 1+
Edge-to-edge mitral valve repair for acute mitral valve regurgitation due to papillary muscle rupture: a case report	Papadopoulos <i>et al.</i> [19]	Anterior STEMI, successful primary PCI of intermediate artery Partial rupture of the anterolateral papillary muscle with flail of A1-A2 and P1	85-year-old female Log Euroscore = 43% STS score = 13% LVEF = 40%	Cardiogenic shock and pulmonary edema IABP and inotropes	2 clips (A2-P2, A1-P1) with a "zippering" of the lateral commissure MR grade = 1-2+ MV area = 2.1 cm ² MV MG = 6 mmHg	Device success	Alive (postop day 7)	20-month NYHA II MR grade = 2+ MV MG = 6 mmHg
One-stop-shop totally percutaneous approach for severe aortic and mitral regurgitation in cardiogenic shock	Pagnotta <i>et al.</i> [37]	Latecomer anterior STEMI, successful primary PCI of proximal right coronary artery and left circumflex artery (proximal left anterior descending artery occluded) Retraction and calcification of posterior mitral leaflet and severe aortic regurgitation in a mediastinal radiotherapy-related valvular heart disease	57-year-old male LVEF = 30% Log Euroscore = 17.7%	Cardiogenic shock IABP and inotropes	1 XTR clip MR grade = 1+ MV MG = 5 mmHg	-	Alive	30-day MR grade = 1+ MV MG = 5 mmHg LVEF = 35%

Successful MitraClip XTR for Torrential Mitral Regurgitation Secondary to Papillary Muscle Rupture as a Complication of Acute Myocardial Infarction	Víllablanca <i>et al.</i> [38]	Lateral NSTEMI, successful primary PCI of proximal and mid-circumflex artery. Complete rupture of posteromedial papillary muscle with flail of P2-P3	70-year-old male LVEF = 60% STS score = 14.3%	Cardiogenic shock and pulmonary edema Impella CP, then exchanged with IABP plus inotropes Mean LAP = 10 mmHg v-wave = 12 mmHg v-wave = 60 mmHg CO = 3.7 L/min CI = 1.8 L/min/m ²	1 XTR clip (A2-P2) MR grade = 1+ MV MG = 1 mmHg Mean LAP = 10 mmHg v-wave = 12 mmHg v-wave = 60 mmHg CO = 3.7 L/min CI = 2.8 L/min/m ²	Alive (postop day 3) NYHA I MR grade = 1+
Transcatheter Mitral Valve Edge-to-Edge Repair with the New MitraClip XTR System for Acute Mitral Regurgitation Caused by Papillary Muscle Rupture	Komatsu <i>et al.</i> [28]	Inferior STEMI, successful primary PCI of culprit single-vessel disease Posteromedial papillary muscle rupture with anteriorly directed eccentric jet Coaptation gap = 1 cm MV area = 6.2 cm ² MV MG = 3 mmHg	55-year-old male LVEF = 55%	Pulmonary edema, cardiogenic shock and acute kidney injury IABP and vasopressors V wave = 50 mmHg V wave = 17 mmHg	2 clip XTR (A2-P2) MR grade = 1-2+ MV MG = 3 mmHg MV area = 2.94 cm ² V wave = 17 mmHg	Alive 3-month MR grade = 2+ (eccentric) No HF symptoms
Case series or registries	Estévez-Loureiro <i>et al.</i> [39]	AMI without papillary muscle rupture: • 2 STEMI • 3 NSTEMI Days between MI and clip: • 8-12 days = 3 pts • 33-49 = 2 pts	N of patients = 5 Age = 51 – 76 years Median Euroscore = 29.1% 5/187 MitraClip procedures (2.7%) Period: 10/2010-01/2015	Cardiogenic shock = 3 NYHA IV = 2 IABP or inotropes = 4 Median sPAP = 62 mmHg	N of clips: • 1 clip = 1 (20%) • 2 clips = 3 (60%) • 3 clips = 1 (20%) MV area > 1.5 cm ² = 5 (100%) MV MG < 5 mmHg = 5 (100%) MR grade M 2+ = 5 (100%)	Deaths = 1 (20%) (due to MOF 1 week after MitraClip) Median sPAP = 38 mmHg No major complications Median follow-up = 317 days NYHA class • I = 1 (20%) • II = 3 (60%) MR grade • 2+ = 2 (40%) • 1+ = 2 (40%)

Percutaneous edge-to-edge mitral valve repair for the treatment of acute mitral regurgitation complicating myocardial infarction: A single centre experience	Adamo <i>et al.</i> ^[40]	AMI without papillary muscle rupture: • 3 STEMI • 2 NSTEMI	N of patients = 5 Age = 73 ± 6 years Males = 3 Median Euroscore = 27.1 ± 13% Median STS score = 10.2 ± 6% 5/79 MitraClip procedures (6.3%) Period: 10/2010-10/2015	Cardiogenic shock = 4 Pulmonary edema = 1 IABP and inotropes = 4 Inotropes = 1	53 ± 33 days from admission N of clips: • 1 clip = 2 • 2 clips = 3	Device success = 5/5	Deaths = 0	1 death due to non-cardiovascular causes 57 days after MitraClip 1 left-ventricular assist device implantation 60 days after MitraClip
	Flint <i>et al.</i> ^[41]	Cardiogenic shock: • AMI = 3 • acute papillary muscle rupture = 1 • chordal rupture = 1 • acute leaflet flail = 1 • acute worsening of functional and degenerative MR = 1 • acute worsening of functional MR = 1	N of patients = 12 Age = 71.7 ± 12.8 Males = 9 LVEF = 46 ± 12% STS score (MV repair) = 33.4 ± 22.3% STS score (MV replacement) = 23.9 ± 18.2% 12/135 MitraClip procedures (9%) Period: 11/2013-10/2018	Cardiogenic shock = 3 - IABP + nitroprusside = 1 - inotropes + nitroprusside = 1 - inotropes = 6 - nitroprusside = 1 - ECMO = 1 Mean LAP = 27 ± 9 Mean PAP = 38 ± 11 Mean sPAP = 57 ± 17 Mean RAP = 13 ± 5 CI = 2.2 ± 0.5 CO = 4.3 ± 1.2	N of clips = 2.3 ± 0.7 MR grade • 0 = 1 • 1+ = 8 • 2+ = 3 MV MG = 5.0 ± 2.7 mmHg LVEDD = 5.4 ± 0.8 cm LVEF = 37 ± 15%	-	Death (6th day) = 1 Resolution of shock = 10 Inotrope-dependent = 1	Deaths = 4 (26-282 days)
Salvage MitraClip in severe secondary mitral regurgitation complicating acute myocardial infarction: data from a multicentre international study	Haberman <i>et al.</i> ^[42]	AMI within 90 days: • 12 STEMI • 8 NSTEMI • 11 anterior • 9 inferior-posterior No evidence of structural valvular damage	N of patients = 20 Age = 68 ± 10 years Males = 6 (30%) LVEF = 35.9 ± 12.5% LVEF < 30% = 7 Period: 01/2011-09/2018	Cardiogenic shock = 8 sPAP = 60 ± 12 mmHg v-wave = 31 ± 25 mmHg	Days after MI = 32 (7-90) Clips = 1-3 MR grade 1+ = 12 MR grade 2+ = 7 PAP = 40 ± 13 mmHg v-wave = 17 ± 5 mmHg	Device success = 19/20 In one patient, a posterior leaflet tear occurred after the second clip implantation and urgent MV replacement surgery was performed but the patient died.	Death = 1	Median follow-up = 15 months Death = 1 (3 weeks after discharge)

Transcatheter mitral valve repair in patients with acute myocardial infarction: insights from the European Registry of MitraClip in Acute Mitral Regurgitation following an acute myocardial infarction (EREMMI)	STEMI <ul style="list-style-type: none"> anterior = 10 (22.7%) inferior = 17 (38.6%) lateral = 10 (22.7%) undetermined = 2 (4.5%) Primary PCI = 30 (68.2%) MR grade <ul style="list-style-type: none"> 3+ = 4 (10.3%) 4+ = 35 (89.7%) MR jet location: <ul style="list-style-type: none"> A1-P1 = 3 (7.5%) A2-P2 = 36 (90%) A3-P3 = 6 (15%) 	N of patients = 44 Age = 70.0 ± 10.8 years Males = 63.6% Euroscore II = 15.1% (6.2-23.2) LVEF = 35% (26-44) LVEDD = 55.5 (48.2-59.5) mm 44/883 MitraClip procedures (5%) Period: 01/2016-12/2018	Mechanical support <ul style="list-style-type: none"> ECMO = 2 (4.5%) IABP = 14 (31.8%) Inotropes = 24 (54.5%) sPAP = 52.5 (25-77.5) mmHg TAPSE = 16.5 (16-20.3) mm	Median n of clips = 2 (1-2) Median MV MG = 3 mmHg (2-4) Median time from procedure = 16 MI = 18 days (13 - (8-27) days 36.8)	Device success = - 86.6% stay after procedure = 16 (18-27) days	30-day Death = 4 (9.1%) Cardiac surgery = 1 (2.3%) 6-month Death = 8 (18.2%) HF rehospital = 8 (18.2%) Cardiac surgery = 3 (6.8%) MR grade <ul style="list-style-type: none"> 0/+ = 31.1% 2+ = 41.4% 3+ = 17.2% 4+ = 10.3% NYHA <ul style="list-style-type: none"> I = 13.8% II = 62.1% III = 17.2% IV = 6.9%
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AMI: acute myocardial infarction; CI: cardiac index; CO: cardiac output; ECMO: extracorporeal membrane oxygenation; HF: heart failure; IABP: intra-aortic balloon pump; LAP: left atrial pressure; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MG: mean gradient; MOF: multiorgan failure; MR: mitral regurgitation; MV: mitral valve; N: number; NYHA: New York Heart Association; NSTEMI: non-ST-elevation myocardial infarction; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention; postop: post-operative; sPAP: systolic pulmonary artery pressure; STEMI: ST-elevation myocardial infarction; STS: Society of Thoracic Surgery; TAPSE: tricuspid annular plane systolic excursion

in cases of cardiogenic shock, intravenous diuretic therapy and non-invasive/invasive ventilation for massive pulmonary edema with acute respiratory distress. Hypertensive or normotensive patients benefit from afterload reduction with intravenous vasodilator therapy, which reduces MR, diminishing pulmonary congestion and increases forward cardiac output^[6].

Then, an accurate trans-esophageal echocardiographic characterization of acute MR is needed to tailor the subsequent actions. The finding of a Carpentier type I lesion, as a leaflet perforation, should lead to exclude an active acute endocarditis, which represents a contraindication for MitraClip procedure and an indication for cardiac surgery^[45]. Clinical context and laboratory tests are pivotal to distinguish active endocarditic processes from a treated state, for which percutaneous interventions are not contraindicated. Careful history taking is sufficient to exclude a device-related (transcatheter prosthetic aortic valves and intracardiac left ventricular assist devices) mechanism.

A Carpentier type II mechanism (leaflet prolapse/flail, rupture of chordae or papillary muscle) warrants a wide differential diagnosis between multiple potential causes. As already reported for Carpentier type I, active endocarditic processes should be excluded, as well. Myocardial ischemia or infarction may cause partial or complete rupture of a papillary muscle and could be targeted with medical therapy or percutaneous myocardial revascularization, before

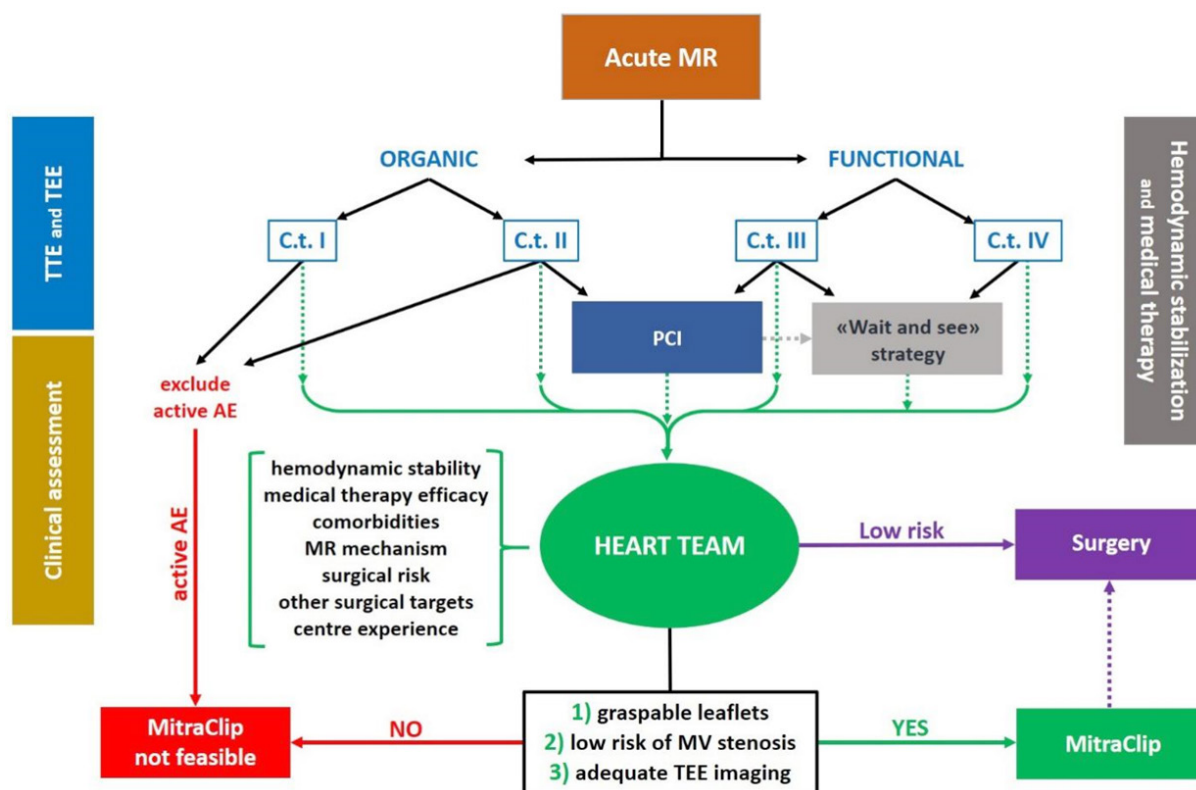


Figure 5. Proposed flow-chart for acute MR decision-making and management. “Carpentier type” refers to Carpentier classification of MR mechanisms, as exposed in Table 1. AE: acute endocarditis; C.t.: Carpentier type; MR: mitral regurgitation; MV: mitral valve; PCI: percutaneous coronary intervention; TEE: trans-esophageal echocardiography; TTE: trans-thoracic echocardiography

treating the MV lesion. A case-by-case judgement is fundamental and should consider the presence of ongoing myocardial ischemia, the timing of onset of myocardial infarction, the extension of coronary artery disease, the type of MV lesion (partial versus complete rupture), and the differential burden between ischemic and valvular diseases. Primary percutaneous coronary intervention for an ST-elevation myocardial infarction is always indicated, except for delayed infarctions without evidence of ongoing ischemia, as they would not yield significant benefits from revascularization and yet be complicated by reperfusion injury^[46,47]. Early surgical intervention is crucial for complete papillary muscle rupture, although partial rupture may benefit from percutaneous revascularization or a brief period of stabilization^[48]. When acute MR is caused by chordal rupture in MV affected by fibroelastic deficiency or Barlow’s disease, anatomic evaluation has a central role to ensure the feasibility of an eventual MitraClip procedure, as already explained in previous paragraphs.

The observation of a Carpentier type III mechanism is related to regional or global LV systolic dysfunction. Medical therapy and percutaneous coronary intervention can acutely reduce the degree of ischemic MR, and an earlier reperfusion time is associated with greater reduction in MR severity^[49]. Thus, if hemodynamic conditions are stable after revascularization or medical therapy implementation, a “wait and see” strategy may be undertaken with close and constant monitoring.

A Carpentier type IV mechanism, namely a SAM of mitral leaflets, observed in hypertrophic and Takotsubo cardiomyopathies, represents an insidious cause of acute MR. Echocardiographic diagnosis is exceedingly important, as vasodilators, inotropes or IABP worsen the clinical and hemodynamic status. Beta-blockers, volume expansion, inotrope discontinuation, afterload augmentation with vasopressors

and lastly mechanical circulatory supports (Impella and extracorporeal membrane oxygenation) are the weapons to turn to^[50,51].

After the initial phases of echocardiographic diagnosis, hemodynamic stabilization, medical therapy implementation and eventually percutaneous coronary revascularization, it is time for Heart Team assessment. Interventionalists, cardiac surgeons, imagers, intensivists and heart failure specialists must meet to tailor the best therapeutic pathway, weighing all clinical and anatomical factors: age, comorbidities, hemodynamic status, response to medical therapy, MR mechanism, surgical risk, other surgical targets and single centre's experience. In cases of low surgical risk, presence of an indication for concomitant cardiac surgery and organic MV disease, cardiac surgery is the first-choice treatment. Differently, in our opinion, MitraClip should be always attempted in a stepwise approach, as it is a safe procedure and does not preclude a delayed surgical intervention. Even in low-risk patients undergoing isolated MV surgery with a low probability of surgical repair, MitraClip may be attempted, above all in high-volume centers. Eligibility for percutaneous edge-to-edge procedure requires only three conditions: possibility to grasp and approximate the leaflets, low risk of MV stenosis, and good-quality TEE imaging^[19].

CONCLUSION

Acute MR is a life-threatening condition, traditionally treated as a medical and surgical emergency. Percutaneous edge-to-edge repair of MV is a safe and effective therapeutic option, does not preclude delayed cardiac surgery and is potentially able to solve almost any type of MV disease, with very few contraindications. Echocardiographic identification of the precise valvular lesion and Heart Team evaluation are pivotal to tailor the best therapeutic pathway for each patient. Literature confirms optimal results of MitraClip in acute MR, but further studies are warranted to shed light on feasibility and limitations of this powerful procedure.

DECLARATIONS

Authors' contributions

Involved in clinical care: Sanz-Sánchez J, Chiarito M, Briani M, Fazzari F, Corrada E, Bragato RM, Pagnotta PA, Regazzoli D

Wrote the manuscript: Cannata F, Regazzoli D

Supervised and coordinated all aspects of the research: Stefanini GG, Reimers B

Contributed to critical revision of the manuscript and approved the final version of the manuscript: Cannata F, Sanz-Sánchez J, Chiarito M, Briani M, Fazzari F, Bertoldi LF, Ferrante G, Corrada E, Bragato RM, Stefanini GG, Pagnotta PA, Reimers B, Regazzoli D

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

A written informed consent for publication was obtained.

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Original Article

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Robot-assisted spleen preserving distal pancreatectomy (RA-SPDP): a single center experience

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Abstract

Aim: To define the outcome of robot-assisted spleen preserving distal pancreatectomy (RA-SPDP) in a high-volume center.

Methods: A retrospective analysis of a prospectively maintained database was performed to identify RA-SPDP performed at our Center between April 2008 to October 2017.

Results: During the study period, RA-SPDP was attempted in 54 patients. The spleen was preserved, always along with the splenic vessels (Kimura procedure), in 52 patients (96.3%). There were no conversions to open or laparoscopic surgery. Mean operative time was 260 min (231.3-360.0). Grade B post-operative pancreatic fistula (POPF) occurred in 19 patients (35.2%). There were no grade C POPF. Two patients required repeat surgery because of postoperative bleeding and splenic infarction, respectively. There were no post-operative deaths at 90 days. Excluding one patient with known diagnosis of metastasis from renal cell carcinoma, malignancy was eventually identified in 7 of 53 patients (13.2%).

Conclusion: In the hands of dedicated pancreatic surgeons, robotic assistance results in a high rate of spleen preservation with good clinical outcomes. Despite careful preoperative selection, several patients can be found to



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have a malignant tumor. Taken altogether these results suggest that patients requiring these procedures should be preferentially referred to specialized centers.

Keywords: Robotic, robot, pancreas, spleen, distal, pancreatectomy, preserving

INTRODUCTION

Based on current evidence, and recommendations, a minimally invasive approach should be offered to patients with benign or borderline tumors located in the body-tail of the pancreas^[1]. Actually, in recent years, distal pancreatectomy gained so much popularity as to be considered the “standard of care” by some authors for resectable pancreatic tumors located in the distal part of the pancreas^[2].

Little doubt exists that the spleen should be preserved, whenever oncologically indicated and anatomically possible, to reduce the rate of infective^[3-5] and thromboembolic complications^[5,6], and to improve blood supply to the proximal part of the stomach^[7]. During distal pancreatectomy the spleen can be preserved along with the splenic vessels (Kimura technique)^[8] or with en-bloc removal of the splenic vessels (Warshaw technique)^[9].

The da Vinci Surgical System® (Intuitive Surgical Inc. Sunnyvale, CA, USA) is a telemanipulator that faithfully transmits the movements of surgeon's hands to the miniaturized tips of intracorporeal instruments with seven degrees of freedom^[10]. Thanks to this tremendous technological improvement, as well as to some other advances, the da Vinci robot was shown to improve surgical dexterity in minimally invasive procedures^[11]. Based on this background the use of the da Vinci robot seems to be particularly rewarding when the spleen and the splenic vessels must be preserved during distal pancreatectomy. We herein present our series of robot-assisted spleen preserving distal pancreatectomy (RA-SPDP).

METHODS

A retrospective analysis of a prospectively maintained database was performed to identify patients who were selected for RA-SPDP and received this procedure between April 2008 to July 2019 at a single Institution (Division of General and Transplant Surgery, University of Pisa). Data were collected and analyzed according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines for observational studies^[12].

Patient selection

Indications to distal pancreatectomy with spleen preservation was established by a multidisciplinary team, annually managing several hundreds of patients with pancreatic diseases. Distal pancreatectomy with spleen preservation was considered in patients with benign tumors causing symptoms or in patients with tumors of low malignant potential located in the body-tail of the pancreas. A minimally invasive approach was considered in each patient unless obviously impossible. A robotic approach was considered whenever the robot was timely available. Alternatively, patients received a laparoscopic procedure. Absolute contraindications to RA-SPDP were thrombosis of the splenic vein, tumors size exceeding 15 cm, concurrent splenic disease, and concerns on tumor type.

All patients underwent standard preoperative work-up and were assigned to one of the risk categories defined by the American Society of Anesthesia^[13]. Pancreatic tumors were studied extensively using a combination of laboratory and imaging studies as required by the individual case until a final diagnosis was agreed upon by a group of experts, including surgeons, oncologists, and radiologists. Endoscopic ultrasound, with fine needle aspiration cytology or biopsy, was also employed as required.

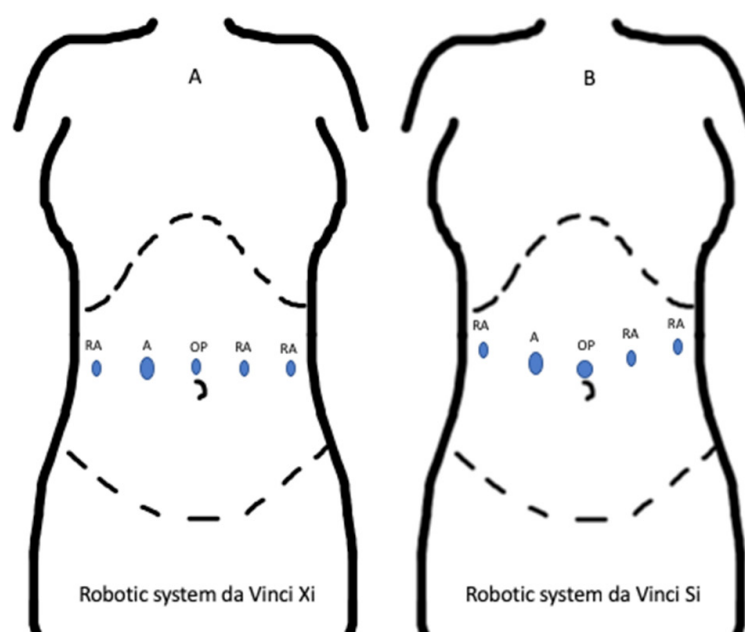


Figure 1. Ports placement. A: ports placement for the robotic system da Vinci Xi; B: ports placement for the robotic system da Vinci Si. RA: robotic arm; A: laparoscopic assistant port; OP: optic port

Surgical technique

Patients were placed supine on an operating table equipped with a thermic blanket with the legs parted (French position). Intermittent pneumatic compression cuffs were placed around the legs and patients were secured to the operating table with wide bandings. The table was oriented in reverse Trendelenburg position (15° - 20°) and tilted to patient's right side (5° - 8°). The patient was then prepped to widely expose the abdomen and a pneumoperitoneum was created and maintained at 10 mmHg. A total of five ports were used: four robotic ports of 8 mm in size and one laparoscopic port of 12 mm in size (to be used by the assistant at the table and accepting an endoscopic stapler), with the da Vinci Xi; three robotic ports of 8 mm in size, one laparoscopic port of 11 mm in size (for the robotic camera) and one laparoscopic port of 12 mm in size, with the da Vinci Si. The optic port was placed just above or below the umbilicus, depending on individual abdominal configuration. The 12 mm port was placed along the right pararectal line^[14,15] [Figure1].

The procedure started by opening the reflection of colon and omentum and mobilizing the left colonic flexure. Next, the peritoneum along the inferior margin of the pancreas was incised and the body-tail of the pancreas was mobilized on the posterior plane. The splenic vein was identified close to the inferior border of the body of the pancreas and clearly visualized before proceeding with further dissections. The common hepatic artery was identified next, as it provided a key landmark for safe division of the pancreas once a tunnel was created behind the pancreatic neck. The origin of the splenic artery was also conveniently identified and encircled with a vessel loop for clear visualization during further dissections and to be available for crossclamping in case of bleeding. The pancreatic neck was divided using either an endoscopic stapler or a combination of dissection devices (with selective ligature of the pancreatic duct and subsequent oversewing of the pancreatic stump). With the splenic vessels in clear view dissection proceeded medial to lateral. Small vein branches were fixed by either energy devices or ligature. Small splenic arteries were all ligated or suture-ligated. Although systematic lymphadenectomy was not performed, lymph nodes around the splenic vessels were removed to permit prognostic stratification in case of unexpected post-operative diagnosis of a malignant tumor. At the end of the procedure the round ligament was mobilized and placed to cover naked vessels close to the pancreatic stump^[16].

Table 1. Baseline characteristics of 54 candidates for RA-SPDP

	Study population
Number of patients (%)	54 (100%)
Median age, years (IQR)	60 (46.5-66)
Gender, male (%)	14 (25.9%)
Median BMI, kg/m ² (IQR)	24.1 (21.6-26.3)
Comorbidity (%)	33 (61.1%)
Pre-operative symptoms (%)	20 (37.3%)
Prior abdominal surgery (%)	28 (51.8%)
Median ASA score (IQR)	2 (2-3)

BMI: body mass index; ASA: American Society of Anesthesiologists

Table 2. Intra-operative outcome measures

	Result
Median operative time, min (IQR)	260 (231.3-360)
Median estimated blood loss, mL (IQR)	150 (100-150)
Patients receiving blood transfusion, <i>n</i> (%)	4 (7.4%)
Median number of blood units transfused per patient (IQR)	1 (1-1)
Conversion, <i>n</i> (%)	0 (0%)
Pancreatic stump closure: stapled, <i>n</i> (%)	6 (11.1%)
Pancreatic stump closure: oversewn, <i>n</i> (%)	48 (88.9%)

When the splenic vessels could not be preserved, or were injured during dissection, before taking the decision to proceed with a Warshaw procedure or with splenectomy, resection and reconstruction or repair were taken into consideration.

Outcome measures

All post-operative events were recorded and classified according to standard outcome metrics^[17-19]. Post-operative pancreatic fistula (POPF) was considered clinically relevant when graded B or C according to the definition of the international study group (ISGPF)^[17]. Complications graded \geq III in the Dindo-Clavien classification were considered severe^[20]. The overall burden of complications was denied using the comprehensive complication index^[21]. Post-operative mortality was considered as any death occurring during the first 90 days after surgery or during the initial hospital stay if longer.

RESULTS

During the study period 54 patients were selected for possible RA-SPDP. The baseline characteristics of these patients are summarized in Table 1.

There was no conversion to open or laparoscopic surgery. The spleen and the splenic vessels were preserved in 52 of 54 patients scheduled for RA-SPDP (96.3%). In three patients the splenic vessels had to be reconstructed to avoid a Warshaw procedure or a splenectomy. There were two elective reconstructions, caused by difficult detachment of the splenic vessels from the tumor, and one urgent reconstruction due to injury to the splenic vein. Overall, one splenic artery was reconstructed by end-to-end anastomosis and two splenic veins were reconstructed using an autologous interposition graft. A summary of intraoperative outcome measures is provided in Table 2.

A summary of the main post-operative outcome measures is provided in Table 3.

Some results are worth to be noted. First, only two patients developed severe post-operative complications. Both required repeat surgery to address bleeding and splenic infraction, respectively. The first patient was

Table 3. Post-operative outcome measures

	Result
Median length of hospital stay (days) (IQR)	10 (8-13)
Median CCI, <i>n</i> (IQR)	20.9 (0-20.9)
Postoperative complications, <i>n</i> (%)	
Clavien-Dindo Grade 0	21 (38.9%)
Clavien-Dindo Grade I-II	32 (59.3%)
Clavien-Dindo Grade III-IV	1 (1.8%)
Post-operative blood transfusions, <i>n</i> (%)	5 (9.2%)
POPF, <i>n</i> (%)	27 (50%)
Grade BL, <i>n</i> (%)	8 (14.8%)
Grade B, <i>n</i> (%)	19 (35.2%)
Grade C, <i>n</i> (%)	0
Clinically relevant POPF, <i>n</i> (%)	19 (35.2%)
PPH, <i>n</i> (%)	1 (1.8%)
Grade A, <i>n</i> (%)	0
Grade B, <i>n</i> (%)	1 (1.8%)
Grade C, <i>n</i> (%)	0
DGE, <i>n</i> (%)	3 (5.5%)
Grade A, <i>n</i> (%)	1 (1.8%)
Grade B, <i>n</i> (%)	2 (3.7%)
Grade C, <i>n</i> (%)	0
Reoperation, <i>n</i> (%)	2 (3.7%)
Readmission, <i>n</i> (%)	4 (7.4%)

CCI: comprehensive complication index; POPF: postoperative pancreatic fistula; DGE: Delayed gastric emptying; PPH: post-pancreatectomy hemorrhage

re-operated during the initial hospital stay, the bleeding was controlled, and the spleen was preserved. The second patient was re-operated at the time of hospital readmission. Overall, the median Comprehensive Complication Index was 20.9 (IQR: 0-20.9). Second, there were no grade C POPF, despite grade B POPF was observed in 19 patients (35.2%). Third, four patients were readmitted (7.4%).

Tumor types are reported in [Table 4](#).

Median tumor size was 26 mm IQR: (20-40). Excluding a patient with known diagnosis of metastasis from renal cell carcinoma, 53 patients were scheduled for RA-SPDP for tumors presumed to be benign, or not overtly malignant. Malignancy was instead discovered in 7 patients (13.2%) [[Table 5](#)].

There were no cases of margin positivity (at 1 mm), in the group of patients with malignant tumors, and the mean number of examined lymph nodes was 13.2 ± 12.3 . Lymph nodes were positive in 3 patients with neuroendocrine cancer. Among a group of 10 patients with intraductal mucinous papillary tumors (IPMN) and worrisome features^[22], two were found to be overtly malignant and of pancreatobiliary type. In one of these patients the tumor was in-situ. In the other patient showed focal infiltration of pancreatic parenchyma (T1). This patient was re-operated three months after the initial surgery to receive splenectomy and completion of the procedure according to oncologic principles. Repeat surgery was performed again using a robotic approach. Additional tissues removed showed no residual malignant growths either in the segment pancreatic body left behind at the initial surgery or in 22 retrieved lymph nodes.

After a mean follow-up period of 48.6 ± 30.6 months no patient developed evidence of either tumor recurrence (for those with a malignant histology) or splenic vein thrombosis (excluding the patient who required splenectomy due to splenic infarction).

Table 4. Histology of resected pancreatic tumors

Tumor types	Number (%)
IPMN, <i>n</i> (%)	10 (18.5%)
Malignant-IPMN, <i>n</i> (%)	2 (3.7%)
MCN, <i>n</i> (%)	10 (18.5%)
Malignant-MCN, <i>n</i> (%)	1 (1.8%)
SCA, <i>n</i> (%)	17 (31.5%)
RCC metastases, <i>n</i> (%)	1 (1.8%)
NET, <i>n</i> (%)	9 (16.6%)
NEC, <i>n</i> (%)	4 (7.4%)

IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystadenoma; SCA: serous cystadenoma; RCC: renal cell carcinoma; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma

Table 5. Detailed histology of malignancies

Tumor types	Histotype	T	<i>n</i>	Grading	Ki67 (%)
Malignant-IPMN					
Branch duct	Pancreatobiliary, with foci of invasive adenocarcinoma	1	0	-	-
Branch duct	Pancreatobiliary, with <i>in-situ</i> adenocarcinoma	-	-	-	-
Malignant-MCN					
	<i>In-situ</i> cystadenocarcinoma	-	-	-	-
NEC					
1	-	3	1	1	1
2	-	3	1	2	5
3	-	2	0	2	8
4	-	2	1	2	7

IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystadenoma; NEC: neuroendocrine carcinoma

DISCUSSION

Minimally invasive distal pancreatectomy is gaining momentum^[23]. The technique for minimally invasive distal pancreatectomy is indeed less demanding than the one required for minimally invasive pancreatoduodenectomy, so that virtually all pancreatic surgeons, and most general surgeons, can perform this procedure safely in the absence of hostile anatomy and/or advanced tumor stage. However, minimally invasive distal pancreatectomy is a quite rare operation, even at high volume centers^[24], requiring careful patient selection^[25] and the ability to fully master minimally invasive techniques^[26]. Patient selection is required to avoid either unnecessary procedures in patients with benign lesions with limited risk of malignant degeneration^[27], or to plan the most appropriate therapeutic strategy for patients with pancreatic cancer^[28]. Mastering of surgical technique is required to adapt the procedure to tumor type, and to face complex intraoperative scenarios that are sometimes unexpected. Minimally invasive spleen preserving distal pancreatectomy is the perfect example of this paradigm as it requires both extra careful patient selection and fine surgical technique. The robot, in competent hands, is a useful tool to improve surgical precision and maximize the rate of spleen preservation. However, it cannot surrogate for competency and basic surgical technique. Preservation of the spleen along with the splenic vessels requires fine dissection and the ability to safely manage small pancreatic vessels. The learning curve for this procedure has not been defined but is expected to be longer than the one reported for distal pancreatectomy with en-bloc splenectomy^[15]. So far, unfortunately, there is also no validated program for systematic training of novices. While International Societies are working on these programs, background experience with other robotic procedures, video review, procedure observation, on-site proctoring (possibly using the dual console), and careful selection of patients are all believed to be important to permit safe implementation of a program for RA-SPDP.

Our series confirms that RA-SPDP is feasible in most patients, when selected appropriately, with a high probability of spleen preservation and a low incidence of severe complications. Admittedly, we have approximately 20 years of experience in minimally invasive distal pancreatectomy^[29], we have performed approximately 400 robotic pancreatectomies, and we treat hundreds of new patients each year with surgical diseases of the pancreas and the periampullary region.

While robotic assistance is certainly associated with increased costs and longer operative times^[30-32], there is no doubt that the use of da Vinci Surgical System enhances surgeon's ability to preserve the spleen during distal pancreatectomy^[33,34]. In this respect we believe that the robot is particularly useful when the Kimura technique is adopted as it allows safe dissection and preservation of splenic vessels. Although the Warshaw procedure can be considered when the splenic vessels cannot be preserved, the overall results of this operation are inferior to those of the Kimura procedure^[35] making preservation of the splenic vessels preferable, whenever feasible. In this respect our experience is quite unique as we had never to adopt the Warshaw procedure, that was instead adopted in 28% to 50% of the patients in other robotic series^[36,37].

We have previously reported that in our hands the risk of unintentional resection of a serous cystadenoma not causing symptoms was 2.1%^[38].

We wish here to underscore that asymptomatic patients with a known diagnosis of serous cystadenoma should not undergo resection regardless of the size of the tumor. We wish also to emphasize that availability of robotic technology and ability to perform a minimally invasive procedure sparing the spleen is not a reason to expand indications to resection. The seemingly high rate of resected serous cystadenomas should therefore be read in the light of the high selection applied to patients reported herein to include only patients with presumably benign tumors. If the same figures were put in the context of our general activity, the rate of resected serous cystadenomas would not exceed 5%.

Our results underscore the importance of patients' selection, not only from the perspective of spleen preservation but also, and perhaps even more importantly, because of the risk of missed malignancy. In our series we found that tumors initially thought to be pre-malignant were instead already overtly malignant in 7 patients (13.2%). Some of these tumors were either in situ or low-grade, so that RA-SPDP could be adequate anyway. On the other hand, we had a case of invasive pancreaticobiliary IPMN and four cases of neuroendocrine carcinoma with lymph nodes metastasis. In these patients the oncologic issue is not to have left the spleen behind, but having spared the splenic vessels and, possibly, having not performed an adequate lymphadenectomy. Indeed, spleen preservation, but using the Warshaw technique, was recently proposed even for pancreatic cancer considering that lymph node metastasis in the splenic hilum are exceedingly rare^[39]. Sparing the splenic vessels, instead, could leave behind microscopic tumor residual (R1 resection). Although this was not the case in our series, even at the level of vascular beds, the risk is real. Our policy of systematic lymph node clearance around splenic vessels permitted to have a clearer picture of the tumor stage, so that we could decide how to manage these cases based on sound data. However, if the malignant tumor is in the body of the pancreas, several lymph node stations are not cleared (such as station number 9) that could harbor metastatic lymph nodes.

In this series we have rarely employed a stapler to divide the pancreas. We have rather preferred to divide the gland sharply while identifying and ligating selectively the pancreatic duct. There is no agreement on the ideal technique for pancreatic transection and closure during distal pancreatectomy^[1]. During the first part of our experience, after sharp division of the pancreas the duct was selectively ligated, and the stump closed with interrupted sutures. Later, thanks to the availability of robotized laparoscopic staplers (namely the SigniaTM power handle and the iDriveTM - Minneapolis, Medtronic, Covidien) we converted to the use of these devices. The stapler was handled and fired by the assistant at the table. The size of the cartridge

was decided based on the thickness of the pancreatic parenchyma. In most patients a purple cartridge reinforced with a bioabsorbable line reinforcement.

Robotic assistance allows to do this as easily as in open surgery, especially when the pancreatic body is partially spared and the pancreas is not divided at the neck, where the stapler should be ideally applied to achieve the best results. While in malignant tumors there is no good reason to spare a portion of the pancreatic body, in benign or pre-malignant tumors parenchymal sparing distal pancreatectomy can be conveniently adopted to reduce the metabolic and digestive consequences of partial pancreatectomy. The literature shows that incidence and severity of POPF are similar irrespective of which surgical technique is used^[40]. Therefore, it is not surprising that robotic assistance does not reduce the occurrence of this complication.

In conclusion, robotic assistance, although not essential, is important to maximize the probability of spleen preservation along with the splenic vessels. RA-SPDP is also associated with a low conversion rate and a limited incidence of severe post-operative complications.

DECLARATIONS

Authors' contributions

Conception and design: Kauffmann EF, Boggi U

Provision of study materials or patients: Kauffmann EF, Napoli N, Menonna F, Genovese V, Cacace C, Gianfaldoni C, Vistoli F, Boggi U

Collection and assembly of data: Kauffmann EF, Napoli N, Menonna F, Genovese V, Cacace C, Gianfaldoni C, Vistoli F, Amorese G, Boggi U

Data analysis and interpretation: Kauffmann EF, Menonna F, Boggi U

Manuscript writing: Kauffmann EF, Napoli N, Menonna F, Genovese V, Cacace C, Vistoli F, Amorese G, Boggi U

Final approval of manuscript: Kauffmann EF, Napoli N, Menonna F, Genovese V, Cacace C, Gianfaldoni C, Vistoli F, Amorese G, Boggi U

Availability of data and materials

Data are stored in a database at University of Pisa.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study was approved by the local ethic committee.

Consent for publication

The informed consent of the person in the video was obtained.

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Review

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The technique of robotic lobectomy I: right-sided lobes

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Abstract

Robotic Lobectomy has been evolving over the past decade and is an oncologically efficacious procedure. Although robotic lobectomy is performed more frequently around the world, it accounts for a small percentage of all lobectomies. The major determinants for the lower level of adoption of the robotic lobectomy procedure are 1. The lack of concise step by step procedure outlines for the surgeons who are transitioning from either open or video-assisted thoracic surgical procedures to robotics, or 2. A strategy for control of catastrophic bleeding during the robotic lobectomy procedure. The Technique of Robotic Lobectomy Part I outlines a stepwise approach to robotic lobectomy for the right upper, middle, and lower lobes. Part II outlines a stepwise approach to robotic lobectomy for left upper, and lower lobes. Part III outlines a methodical technical approach for the control of catastrophic bleeding complications.

Keywords: Robotic, lobectomy, bleeding, upper lobectomy, middle lobectomy, lower lobectomy, lung cancer

INTRODUCTION

The most common indication for lung resection is lung cancer. Approximately 228,150 (116,440 in men and 111,710 in women) new cases of lung cancer were diagnosed in the United States in 2018. During the same period, 142,670 patients died from lung cancer (76,650 in men and 66,020 in women)^[1] Lung cancer is by far the leading cause of cancer death among both men and women. Each year, more people die of



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lung cancer than of colon, breast, and prostate cancers combined. The overall five-year survival for lung cancer is approximately 23%. This dismal outlook is due, largely, to the fact that over 50% of patients are in stage III and IV at the time of diagnosis. On the other hand, the five-year survival for patients with stage I disease is 80%-95%. Besides, it is estimated that at any one time approximately 650,000 patients with early lung cancer remain undiagnosed. Lobectomy is indicated as the treatment for early-stage lung cancer.

The first report of the use of the Robotic System for lobectomy in the treatment of primary lung cancer came from Melfi *et al.*^[2] in 2002. Due to safety concerns, the surgery was converted to a thoracotomy in two of five patients. Nevertheless, the report demonstrated the feasibility of the procedure. The first robotic lobectomies were reported in 2003 by Morgan *et al.*^[3] and Ashton *et al.*^[4].

In 2006 Park *et al.*^[5] reported Robot-assisted thoracoscopic Surgery (RATS) technique which represented a hybrid procedure. In 2009, Gharagozloo *et al.*^[6] reported a series of 100 consecutive patients who underwent the RATS procedure which was performed as a hybrid operation using robotic dissection on a video-assisted thoracic surgical (VATS) platform. In the same year, Veronesi *et al.*^[7] described a modified RATS technique with the use of 4 robotic arms. Since that report, the robotic surgical systems and instruments have evolved and the procedures have become more standardized, such that in 2015, over 6000 robotic lobectomies were performed in the United States^[8].

Several factors have been responsible for the greater acceptance and use of robotics for lobectomy: (1) introduction of robotic dissecting instruments such as the Endotip Bipolar Dissector (curved tip bipolar), Vessel Sealer, Endowrist Staplers (curved tip vascular stapler) have facilitated dissection and vascular control; and (2) the newer robotic surgical platform (DaVinci Xi) which has given active control of stapling to the surgeon and relegated the bedside assistant to the more passive role of instrument exchange and specimen retrieval.

More recently, a four-arm completely port-based robotic lobectomy technique (CPRL) was reported by Cerfolio *et al.*^[9]. This technique is much simpler and more standardized and can be adapted for all the lobes. It also allows for relatively more efficient use of the assistant port by the bedside surgeon.

CPRL has become the technique of choice for lobectomy as it is completely port-based, uses 4 arms, and CO₂ insufflation. Both Si and Xi da Vinci platforms can be used. As described by Cerfolio *et al.*^[9], with the da Vinci Si system, the procedure uses three 8-mm ports (left and right robotic arm ports, fourth robotic arm port), and a 12-mm port (camera). With the Si system, many surgeons also use a 12-mm assistant port that can be used for stapling, occasional suction, specimen retrieval, and exchange of items such as rolled-up sponges and vessel loops. The assistant port is also important for the management of bleeding in the event of a pulmonary artery or vein injury. With the Xi system, three of the ports are 8-mm ports, and the 4th is a 12 mm, however, the camera port and the right and left arm ports are 8 mm, and the 12 mm port is used for the introduction and firing of the robotic Endowrist stapler.

Gharagozloo *et al.*^[10] reported their experience with 638 consecutive robotic lobectomies for early-stage lung cancer. Median operative time was 176 min (range 160-456), Median Chest tube time was 3 days (2-8 days), Median air leak time was 0 (0-3 days), Median length of stay was 3 days (1-26 days). Minor complications were observed in 133 patients (21%). The most common complication was atrial fibrillation which was seen in 13% of patients. Thirteen (2.1%) patients had major complications, including bronchopleural fistula (3), pulmonary embolism (5), acute renal insufficiency (3), hemorrhage (2). Conversion to a thoracotomy occurred in 11 (1.7%) patients. 6/11 conversions were for bleeding. The other conversions (5/11) was due to anatomic and oncologic reasons. There were 3 deaths (0.5%). All 3 deaths occurred in the first 20 patients and during the learning curve of the procedure. This was attributed to

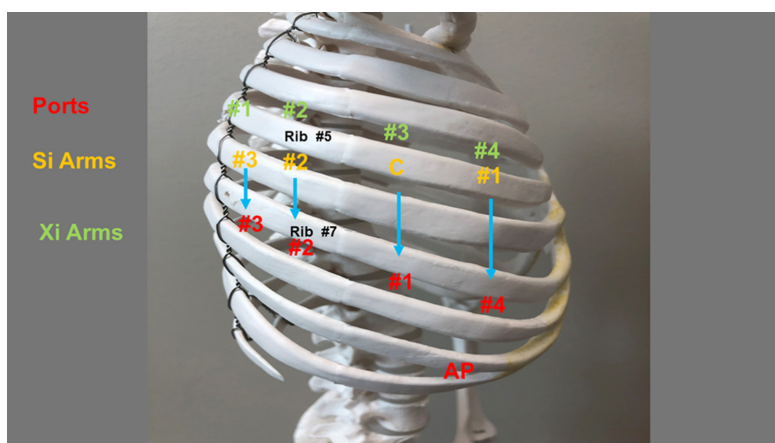


Figure 1. Port placement for robotic lobectomy in the right chest. AP: assistant port

poor patient selection, lack of surgeon and team experience, and rudimentary robotic instruments for the lobectomy procedure. There were no deaths in the last 618 robotic lobectomy procedures. Meyer *et al.*^[11] have reported that based on an assessment which included operative times, surgeon comfort, and mortality, the learning curve of robotic lobectomy was 18 ± 3 cases.

The technique of robotic lobectomy is presented in three consecutive papers: Part I outlines a stepwise approach to robotic lobectomy for the right upper, middle and lower lobes. Part II outlines a stepwise approach to robotic lobectomy for left upper, and lower lobes. Part III outlines a methodical technical approach for the control of catastrophic bleeding complications.

RIGHT-SIDED LOBECTOMY

Port placement

The operating room table is reversed such that the pedestal does not interfere with the docking of the robot over the head of the patient.

A Double Lumen tube is placed, and the patient is positioned in a full lateral decubitus position. The right arm is placed over pillows and positioned high enough such that access to the 4th intercostal space in the anterior axillary line is readily attained. The table is flexed to move the hip down and to open the intercostal spaces. The lung is deflated and placed on suction. The position of the double-lumen tube is rechecked after the patient is prepped and draped.

Figure 1 shows the right chest port placement. A line is drawn from the tip of the scapula to the costal arch. This delineates the highest point in the chest and the mid scapular line (posterior axillary line). Pleural entry is with a Hassan Needle. Saline is infused and care is taken to look for easy egress of the saline from the needle. If there is any question of pleural adhesions, we use a Visiport Instrument (Medtronic Inc. Norwalk, Conn) for entry into the pleural space under direct vision. If the Visiport is used, a purse-string is placed in the muscle layer and tied around the robot camera port to prevent CO₂ leakage.

Port #1 is the camera port. Warm, humidified CO₂ is insufflated through this port at a flow of 6 L/min to a pressure of 6-8 mmHg to push the lung and diaphragm away. The other ports are placed under direct vision. Port #2 (8 mm) is placed in the 7th intercostal space in the poster scapular line. This Port is 9 cm posterior to Port #1 and accommodates da Vinci arm #2. Before the placement of Port #3, a 21-gauge needle is inserted into the 7th intercostal space at the costovertebral junction from the patient's back and

injects a 10 mL subpleural bubble of 0.25% bupivacaine with epinephrine near the intercostal nerve. Next, Port #3 is placed 10 cm posterior to Port #2 in the 7th intercostal space just medial to the spine. This port accommodates da Vinci arm #3. Port #4 is placed 9 cm anterior to Port #1 in the 7th intercostal space at the anterior scapular line. This port accommodates da Vinci arm #1. The Assistant Port #5 uses a 10-12 Versiport (Medtronic Inc., Norwalk, Conn, USA) trocar and is placed in the 9th intercostal space and is triangulated between Port #1 and #4. It should be two or three ribs lower than and as distant to the da Vinci ports as possible to maximize the assistant workspace. Keeping this port off the trajectory lines for the other ports will facilitate the patient-side assistant's access for the retraction and other maneuvers. In all, including the vitally important Assistant Port, lobectomy is performed with five ports. The use of additional ports should be tailored to the specific situation and the experience of the surgeon. Surgeons are encouraged to use as many ports as are necessary to perform a safe and oncologically efficacious lobectomy.

Port placement and intercostal sites are the same for every lobe. All efforts should be made to keep the distance between the ports as close to what has been described above. In smaller patients, care must be taken to keep the trocar sites as far as possible and within the parameters that have been outlined. This strategy prevents interference in arm function with the present robotic platforms. Port placement may be modified in the future with the development of new platforms and robot arms which may have a smaller "footprint" on the chest.

Port Placement with Si Robot: Robotic arm #3 is located two cm lateral from the spinous process of the vertebral body, robotic arm #2 is 10 cm medial to robotic arm #3, the camera port (we prefer the 12 mm camera) is 9 cm medial to robotic arm 2, and robotic arm #1 is placed right above the diaphragm anteriorly.

Port Placement with Xi Robot: For the Xi system, the ports are placed in slightly different locations. They are also numbered differently due to the system. Robotic arm #1 is placed 4 cm away from the spinous process. Robotic arm #2 is placed 8 cm from arm #1 and robotic arm #3 is placed 8 cm from arm #2. Robotic arm #4 is placed right above the diaphragm anteriorly. The assistant port is triangulated behind the camera arm and robotic arm #4 in a similar fashion. The camera is carried by arm #3. Arms #1 through #4 are all placed in the 7th intercostal space.

Instruments: 0° and/or 30° down viewing endoscope, 5 mm Thoracic Grasper (left ③), Cadere Forceps (left ②) and Curved Bipolar Dissector (right ①).

Begin by dividing the inferior pulmonary ligament and remove station #9, and #8 nodes [Figures 2 and 3]. Next, the most posterior arm is used to retract the lower lobe medially and anteriorly to remove lymph nodes from station #7. Next, open the pleura anterior to the vagus nerve and divide the anterior branch of the nerve which traverses the subcarinal space. At the beginning of the case, a nasogastric tube should be inserted to decompress the stomach. After decompression of the stomach, some surgeons may prefer to remove the nasogastric tube to aid in the retraction of the esophagus during the subcarinal dissection. This opens the subcarinal space and allows for better access to the Station #7 nodes. Identify the right mainstem bronchus and stay posterior to the edge of the cartilage. Remove the station #7 nodes and control the subcarinal artery at the carina. At the end of the dissection, the right and left mainstem bronchi should be visible, and the posterior aspect of the pericardium should be cleaned and visible [Figure 4]. Next, the most posterior arm is used to retract the upper lobe inferiorly during dissection of stations 2R and 4R, clearing the space between the superior vena cava (SVC) anteriorly, the trachea posteriorly, and the azygos vein inferiorly [Figure 5].

Completion of the lymph node dissection opens the mediastinal space and facilitates the dissection of the artery and the bronchus. The key to the safe dissection of the posterior aspect of the artery, vein, and

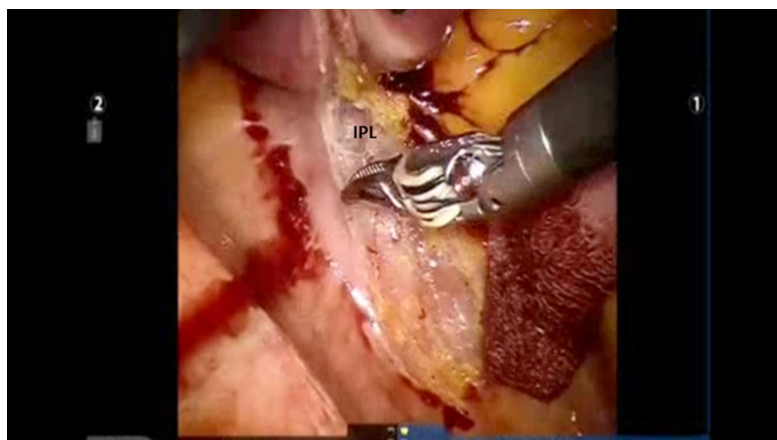


Figure 2. Begin by dividing the IPL. IPL: inferior pulmonary ligament

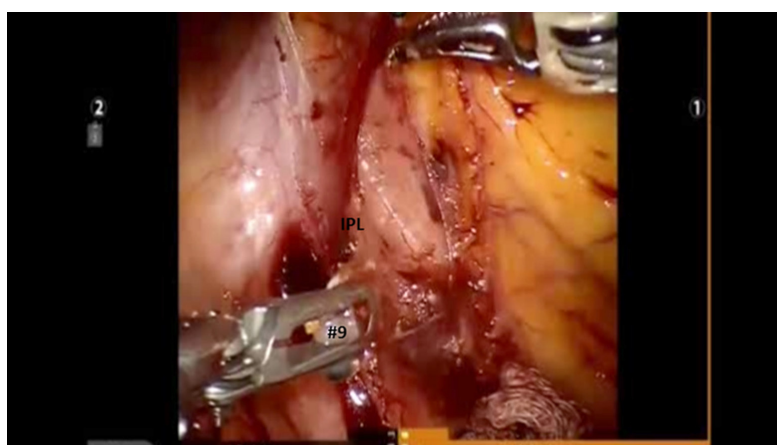


Figure 3. Remove station # 9, and #8 nodes. IPL: inferior pulmonary ligament

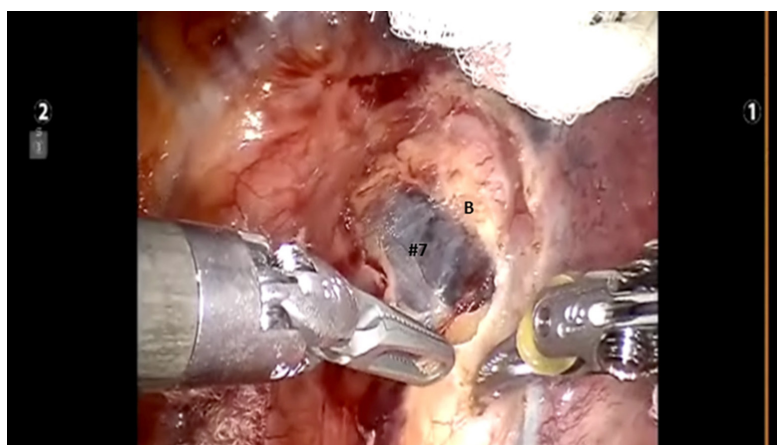


Figure 4. Identify the right mainstem bronchus and stay posterior to the edge of the cartilage. Station #7 nodal bundle is removed

bronchus is a wide dissection of the mediastinal nodal tissue. The artery, vein, and the bronchus must be encircled under direct vision and after complete skeletonization. All attempts at blunt or blind dissection are strongly discouraged. Not only will blunt dissection without full mobilization of the structure and

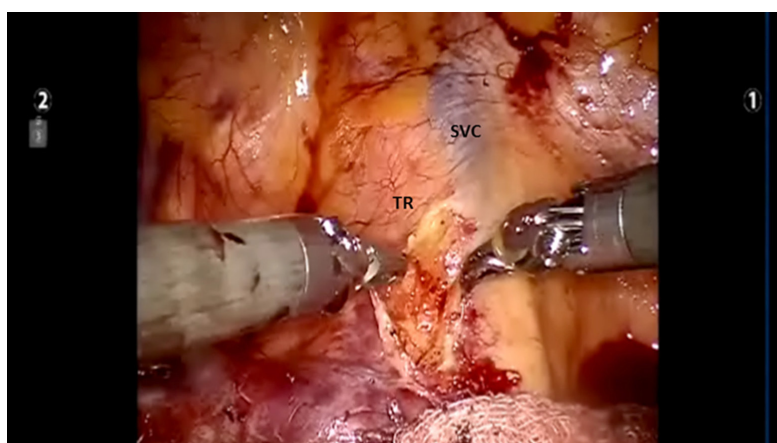


Figure 5. The most posterior arm is used to retract the upper lobe inferiorly during dissection of stations 2R and 4R, clearing the space between the SVC anteriorly, the TR posteriorly, and the azygos vein inferiorly. SVC: superior vena cava; TR: trachea

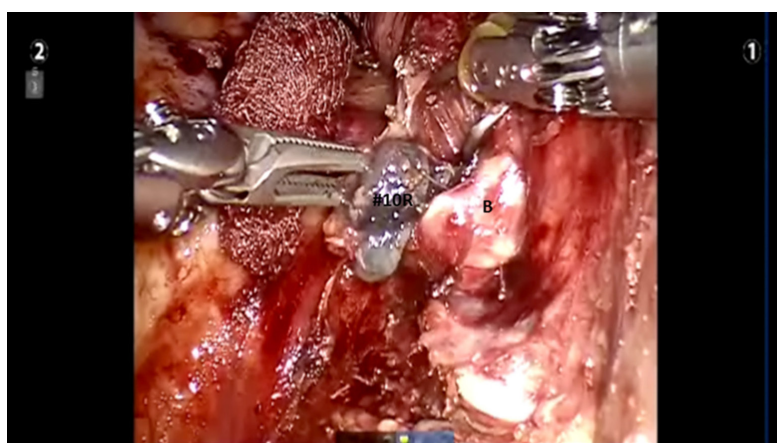


Figure 6. Further dissection of Level #10 node off the upper lobe bronchus (B)

dissection of the surrounding nodal structures result in injury to these vital structures, but also it will repair the injury extremely difficult. After identifying the right mainstem bronchus, it is followed up to the level of station #10R lymph node. This node sits between the truncus branch and the superior pulmonary vein. It should be dissected and swept towards the lung, thereby exposing the truncus branch.

Dissection is continued and the crotch between the right upper lobe (RUL) bronchus and bronchus intermedius is defined. All level #7 nodes and the sump node are removed. This maneuver facilitates later dissection of the pulmonary artery as well as eventual stapling of the RUL bronchus [Figure 6].

Next, the lung is retracted posteriorly to expose the anterior hilum. The dissection is carried down between the hilar structures and the phrenic nerve. The phrenic nerve is swept down to remove the #10R lymph node. The bifurcation between the middle and upper lobe veins is dissected. It is best to encircle the entire upper lobe vein off the underlying pulmonary artery using the Cadere Forceps in the left arm and pass a red rubber vessel loop to elevate the vein. This makes the dissection of the middle lobe vein easier. Following the dissection of the middle lobe vein, the Cadere Forceps is passed under the elevated upper lobe vein, the vessel loop is released and re-grasped thereby isolating the upper lobe vein. Dissection is continued and the proximal main pulmonary artery is exposed as it emerges from the pericardium. The upper lobe vein is divided using a vascular stapler either using the robot arm or passed through the

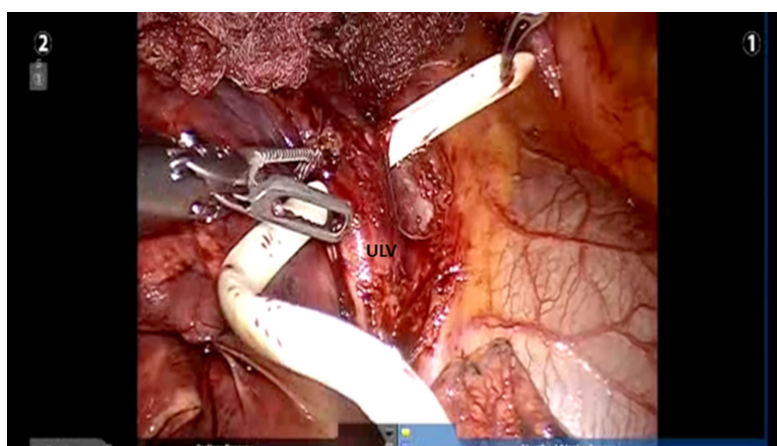


Figure 7. The ULV is elevated, the leader catheter portion of a vascular stapler is passed underneath. ULV: upper lobe vein

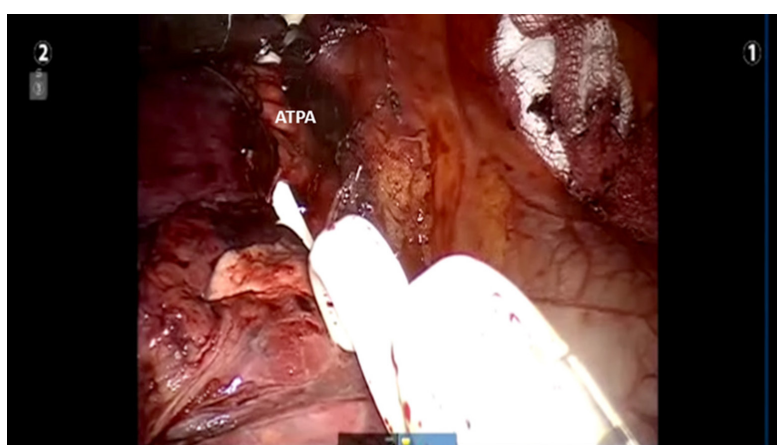


Figure 8. The anterior ATPA branch is elevated, encircled, and the leader catheter portion of a vascular stapler is used to position the stapler. ATPA: apical trunk pulmonary artery

accessory port by the assistant (Covidien Signia gold tip with leader catheter with white 45 cartridges) [Figure 7].

Next, the anterior apical trunk pulmonary artery branch is encircled with a vessel loop and transected with a linear stapler in the same fashion as the vein [Figure 8].

The Lung is once again reflected anteriorly, thereby exposing the posterior aspect of the hilum. The right upper lobe bronchus is identified from a posterior approach and it is separated from the main pulmonary artery which lies underneath. The RUL bronchus is encircled with a vessel loop and transected using a stapler with a green cartridge. Before firing the stapler, the anesthesiologist must make certain that the suction catheter in the endotracheal tube is removed [Figure 9].

After this maneuver, the posterior segmental pulmonary artery is exposed and divided. This vessel is usually smaller than 6 mm and therefore can be divided with a vessel-sealing device and the proximal stump is further reinforced with a small Titanium clip applied with the robotic Endowrist small clip applier.

Next, the fissure between the right upper lobe and the right middle lobe is divided with gold or purple stapler from an anterior to posterior direction [Figure 10]. Finally, the lung is retracted superiorly, the

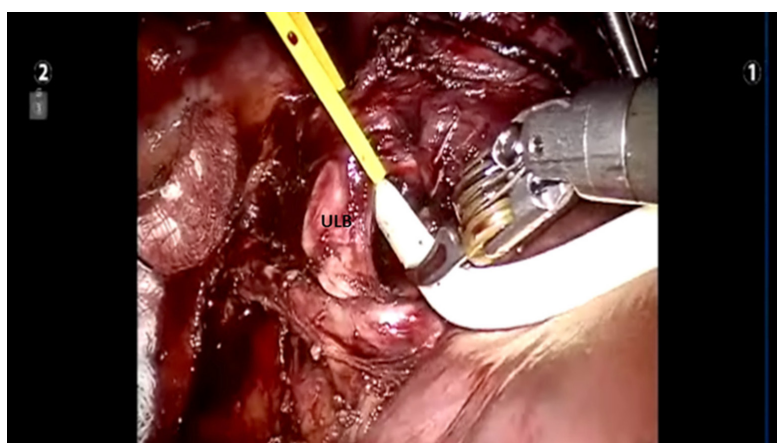


Figure 9. The right upper lobe bronchus is encircled with a vessel loop before passage of the stapler. ULB: upper lobe bronchus

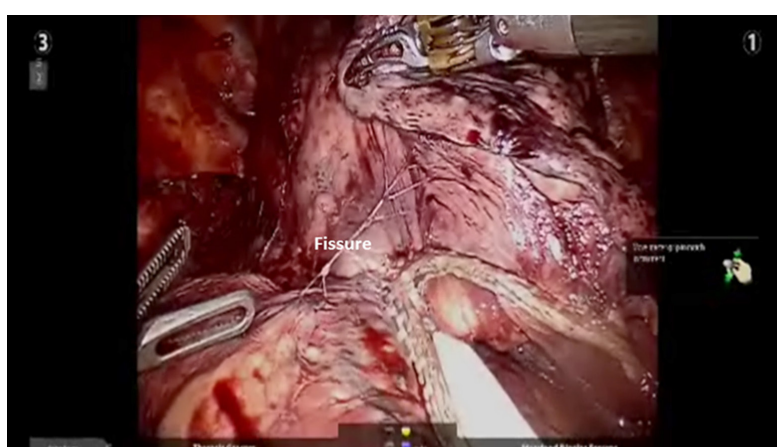


Figure 10. Divided transverse fissure

pulmonary artery is visualized, and the posterior aspect of the fissure (minor fissure) is divided in a similar manner.

The specimen retrieval bag (Anchor Tissue Retrieval System, ConMed Inc. Utica, NY, USA) is introduced through the Accessory port, the specimen is placed into the bag, and the bag is removed.

The dissection begins like that of upper lobectomy by dividing the inferior pulmonary vein and removing station #9, #8, and #7 nodes. Next, the most posterior arm is used to retract the upper lobe inferiorly during dissection of stations 2R and 4R, clearing the space between the SVC anteriorly, the trachea posteriorly, and the azygos vein inferiorly. Completion of the lymph node dissection opens the mediastinal space and facilitates the dissection of the artery and the bronchus.

The pleura posterior to the phrenic nerve is incised. The superior pulmonary vein is dissected in the same manner as with right upper Lobectomy. The bifurcation between the right upper and middle lobar veins is developed by dissecting it off the underlying pulmonary artery. The right middle lobe vein is encircled and divided [Figure 11].

In our experience, the best way to enter the appropriate plane over the pulmonary artery is to follow the anterior segmental branch to the lower lobe. This branch is usually very superficial and is not covered with

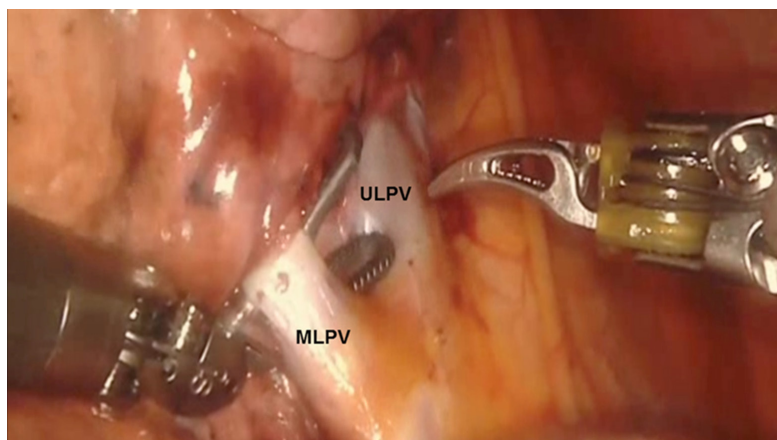


Figure 11. The right MLPV is encircled. ULPV is seen. MLPV: middle lobe pulmonary vein; ULPV: upper lobe pulmonary vein

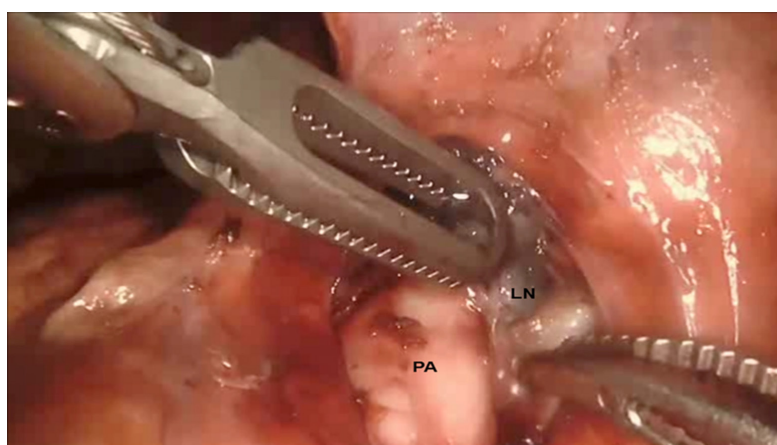


Figure 12. Removal of station #11 nodes off of the pulmonary artery in the fissure. PA: pulmonary artery; LN: lymph node station #11

nodal or parenchymal tissue. This branch can be followed superiorly to the main pulmonary artery. This maneuver helps to elevate station #11 nodes off the pulmonary artery and to identify the artery branch to the middle lobe. Next, the remainder of the fissure between the right middle lobe and right lower lobe is divided in an anterior to posterior direction [Figure 12]. At times there is a vein branch to the middle lobe which drains into the inferior pulmonary vein. This is divided into the remainder of the anterior fissure.

Next, the middle lobe bronchus is identified. It will be running from left to right in the fissure. It is encircled and divided, taking care to avoid injuring the pulmonary artery branches that are located directly behind it [Figure 13].

The middle lobe artery is encircled and divided with a vascular load. At times right middle lobe artery branches come off directly from the main pulmonary artery instead of bifurcating from the common trunk of a single middle lobe artery. These are encircled and divided in the same fashion [Figure 14].

Dissection of the fissure is then continued posteriorly until the main artery trunk and the superior segmental artery branch are identified. After identifying the main artery, the Cadiere forceps in the left hand is used to go under the transverse fissure in a posterior to anterior direction heading for the divided superior pulmonary vein. A vessel loop is passed, and the fissure between the upper and middle lobes is

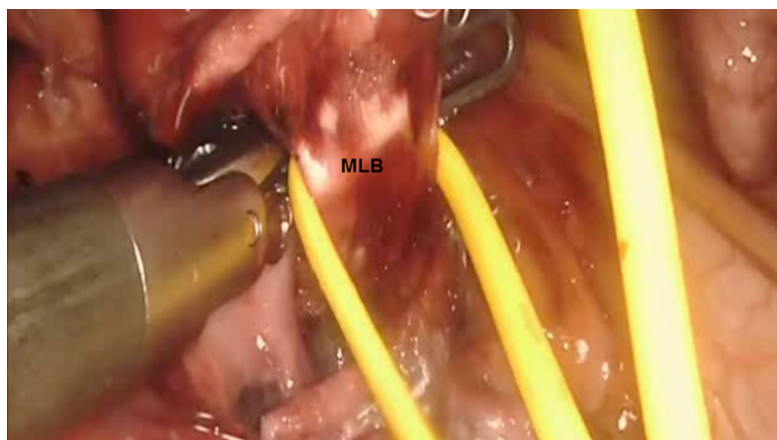


Figure 13. A vessel loop is passed around the MLB and used to elevate it off the pulmonary artery. MLB: middle lobe bronchus

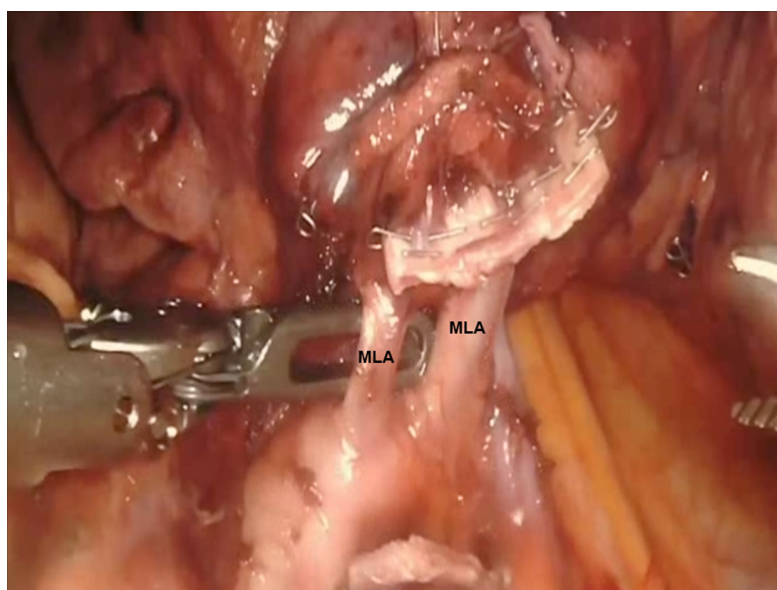


Figure 14. Right middle lobe artery branches (RML) are encircled. MLA: right middle lobe artery branch.

divided using a stapler [Figure 15].

The docking, setup and mediastinal nodal dissection are similar to Right Upper Lobectomy.

Following the mediastinal nodal dissection, the lung is retracted posteriorly and held in place with the robot arm. The bifurcation of the right superior and inferior pulmonary veins is dissected and delineated. The location of the right middle lobar vein should be positively identified to avoid inadvertent transection. The inferior pulmonary vein is encircled using the Cadieere Forceps and divided using a white vascular cartridge.

The anterior branch of the lower lobe pulmonary artery is most superficial and usually does not have overlying nodal tissue. This branch is identified and traced back to the main trunk of the pulmonary artery. Next, the sub adventitial plane overlying the pulmonary artery is developed and nodal tissue (Station #11) is removed. Retraction is released and the lung is allowed to remain in its normal position, thereby facilitating visualization of the oblique fissure. The dissection is carried posteriorly in the sub adventitial

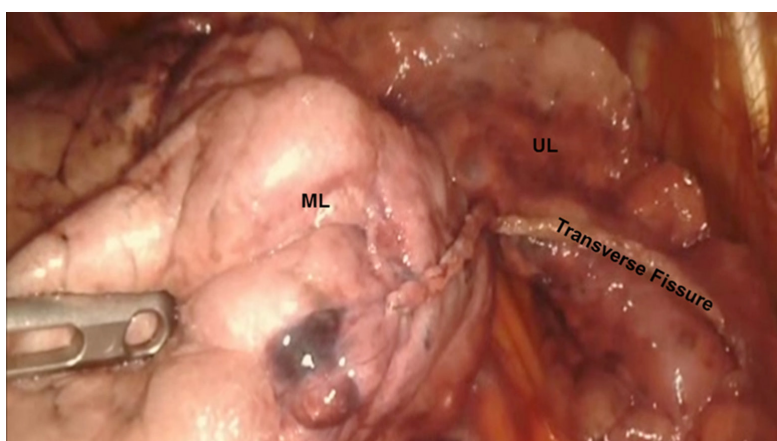


Figure 15. View of the divided transverse fissure. UL: upper lobe; ML: middle lobe

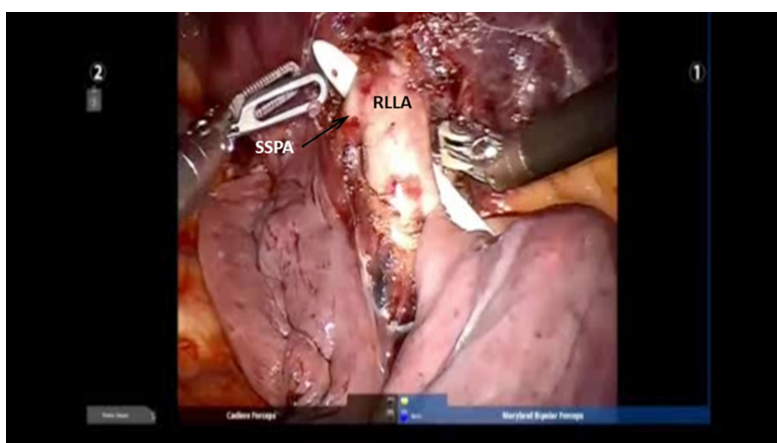


Figure 16. The pulmonary artery branch to the lower lobe (RLLA) is identified. The SSPA is identified. RLLA: right lower lobe pulmonary artery; SSPA: superior segmental artery

layer and the superior segmental branch of the lower lobe pulmonary artery is identified. The major fissure is then divided from an anterior to posterior direction using a stapler which is introduced from the anterior port.

The pulmonary artery branch to the lower lobe is identified. At times the superior segmental pulmonary artery and the inferior lower lobe segmental artery can be taken by encircling the pulmonary artery proximal to the takeoff of the superior segmental artery. Other times these branches need to be taken separately. We prefer to take the inferior segmental artery first, thereby making the encirclement of the superior segmental artery easier [Figure 16].

Next, the posterior aspect of the oblique fissure is divided using a stapler with a purple cartridge. Finally, the bronchus is encircled and divided using a purple cartridge [Figure 17]. The lower lobe is removed as described earlier.

CONCLUSION

Robotic Lobectomy has been evolving over the past decade and is an oncologically acceptable procedure. A methodical approach to the conduct of the lobectomies and a proven strategy for the control of major vascular injury will increase adoption. The technique of Robotic Lobectomy Part II outlines the technique

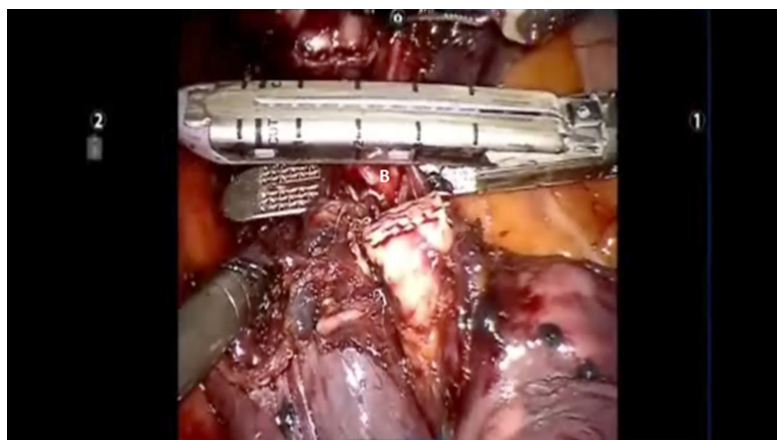


Figure 17. The lower lobe bronchus (B) is divided using with a stapler holding a purple cartridge

of lobectomy for the left-sided lobes. The technique of Robotic Lobectomy Part III outlines the methodical approach for the control of catastrophic bleeding complications.

DECLARATIONS

Authors' contributions

Participated in the research, performed the procedures and wrote the manuscript: Gharagozloo F, Meyer M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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The technique of robotic lobectomy II: left sided lobes

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Abstract

Robotic lobectomy has been evolving over the past decade and has been shown to be an oncologically efficacious procedure. The Technique of Robotic Lobectomy I outlined the stepwise approach to robotic lobectomy of the right upper, right middle and right lower lobes. This paper outlines the stepwise technical approach to robotic lobectomy of the left upper and lower lobes. The accompanying paper, Technique of Robotic Lobectomy III: Control of Bleeding Complications, outlines a methodical technical approach for the control of catastrophic bleeding complications.

Keywords: Robotic, lobectomy, bleeding, upper lobectomy, lower lobectomy, lung cancer

INTRODUCTION

Cerfolio reported the technique of four-arm completely port-based lobectomy in 2011^[1,2]. This technique has become the standard approach in robotic lobectomy. In the preceding manuscript: Technique of Robotic Lobectomy I, we outlined the stepwise approach to robotic lobectomy of the right upper, right middle and right lower lobes. This paper outlines the stepwise technical approach to robotic lobectomy of the left upper and lower lobes.



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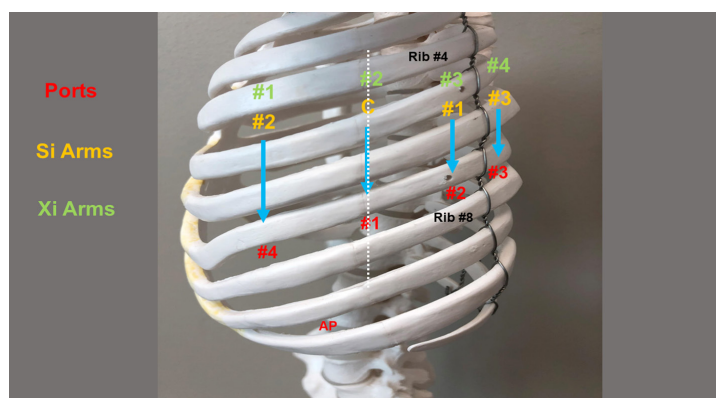


Figure 1. Port placement for robotic lobectomy of the left chest. AP: assistant port

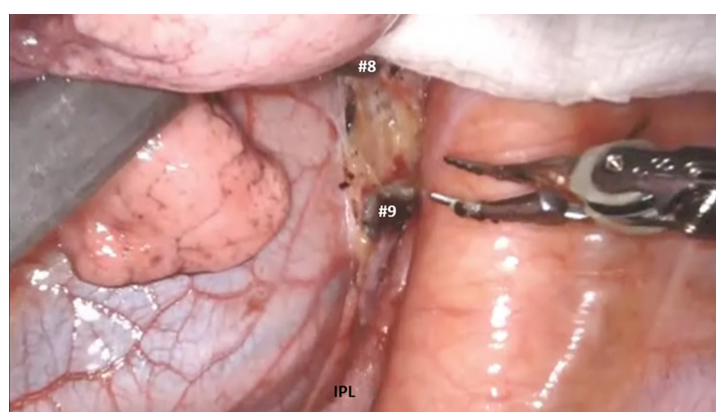


Figure 2. Dissect the inferior pulmonary ligament and remove station #9 and #8 nodes. IPL: inferior pulmonary ligament

LEFT SIDED LOBECTOMY

Left upper lobectomy

Instruments: 0° and/or 30° down viewing endoscope, 5 mm thoracic grasper, Cadiere forceps and curved bipolar dissector.

Figure 1 shows left sided port placement. The technique of port placement is similar to the right side. Begin by dividing the inferior pulmonary ligament and removing station #9 and #8 nodes [Figure 2]. The lung is retracted medially and anteriorly in order to remove lymph nodes from station #7. After the stomach has been decompressed, at this stage, some surgeons prefer to remove the nasogastric tube in order to create a greater space for the subcarinal and mediastinal dissection. Next, open the pleura anterior to the vagus nerve. Identify the left mainstem bronchus and stay inferior to the edge of the cartilage. The station #7 nodal bundle is accessed between the inferior pulmonary vein and the left mainstem bronchus. The nodal bundle is traced to the carina and is then removed [Figure 3]. Next, the lung is retracted inferiorly, and the pleura overlying station #5 nodal bundle is opened in the lower margin of the aortic arch and the superior margin of the left pulmonary artery. Station #5 nodes are removed paying attention to the location of the phrenic nerve [Figure 4].

The left main pulmonary artery is identified above the left main bronchus. The space between the pulmonary artery and the bronchus is opened and station #10L nodal bundle is identified overlying the superior border of the bronchus [Figure 5]. The space between the pulmonary artery and the aorta is

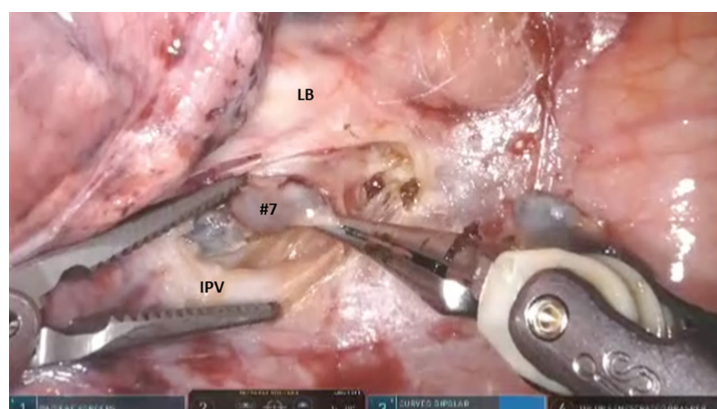


Figure 3. Open the pleura anterior to the vagus nerve. Identify the LB, stay inferior to the edge of the cartilage and remove the nodal bundle of station #7. LB: left bronchus; IPV: inferior pulmonary vein



Figure 4. Station #5 nodes are removed. AO: aortic arch

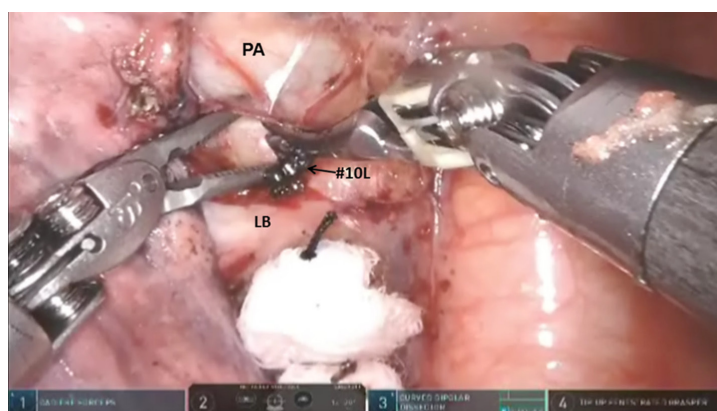


Figure 5. The left main PA is identified above the LB. Station #10L nodes are removed. PA: pulmonary artery; LB: left bronchus

cleared in order to visualize the nodal bundle that encases the apico-posterior trunk of the artery. Care is taken to identify and preserve the vagus and the recurrent laryngeal branch. After exposing the apico-posterior trunk, the nodal bundle (station #10) is swept in an infero-medial direction, thereby exposing the underside of the truncus branch and its takeoff from the main pulmonary artery [Figures 6 and 7]. The bronchus just deep to the artery is identified. This maneuver facilitates the encirclement of the apico-

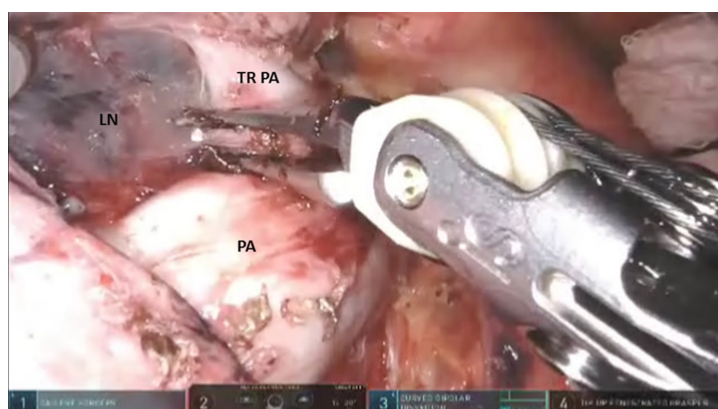


Figure 6. After exposing the apico-posterior trunk (TRPA), the nodal bundle (station #10 LN) is swept in an infero-medial direction. Descending branch of PA. PA: pulmonary artery; TRPA: apico-posterior trunk of left pulmonary artery

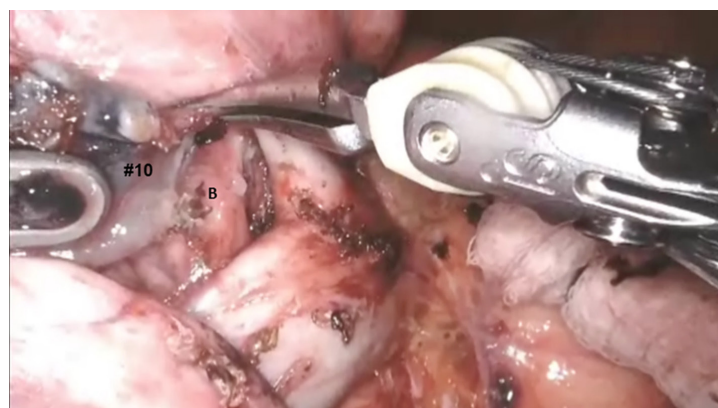


Figure 7. After removing station #10 lymph nodes, the bronchus (B) is identified just deep to the artery

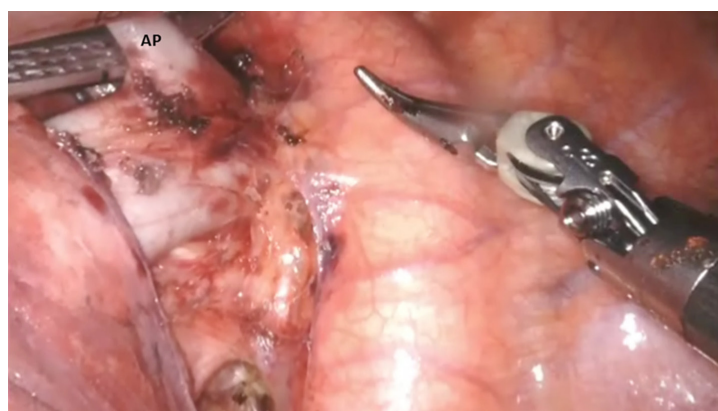


Figure 8. The apical branch of the pulmonary artery (AP) branch is then encircled and divided using a stapler with a white vascular cartridge. AP: apical branch of pulmonary artery

posterior branch using the Cadieere forceps in the left robotic hand. The pulmonary artery branch is then divided using a stapler with a white vascular cartridge [Figure 8].

Next, the upper lobe and lower lobe are retracted in opposite directions and the fissure is identified. Dissection of the nodal bundle in station #11 allows for the identification of the pulmonary artery in the

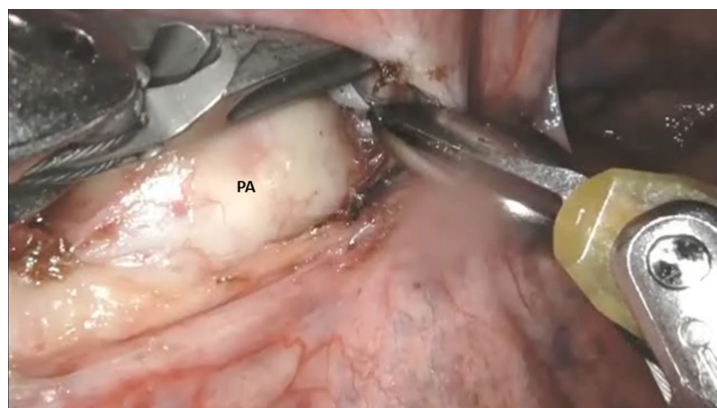


Figure 9. In the main fissure, the sub adventitial plane over the PA is entered, and dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure towards the main PA. PA: pulmonary artery

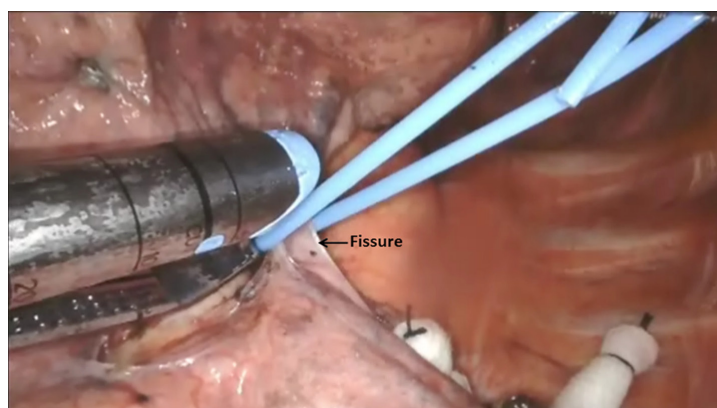


Figure 10. A vessel loop is passed under the posterior aspect of the fissure, the pulmonary parenchyma is elevated and divided with a stapler carrying a blue load

fissure. The artery is most superficial at the junction of the lingula, upper lobe and the lower lobe. The sub adventitial plane is entered, and dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure toward the main pulmonary artery [Figure 9]. The Cadere forceps is used to pass a vessel loop under the pulmonary parenchyma in the posterior aspect of the fissure. A stapler with a blue cartridge is used to divide the tissue in the posterior aspect of the fissure [Figure 10]. The sub-adventitial plane is then developed anteriorly in order to identify the lingular branch of the pulmonary artery. The artery is encircled and divided in a similar fashion with a white cartridge [Figure 11]. Following the division of the lingular artery, the remainder of station #10L node is removed off the underlying bronchus.

Next, the lung is retracted posteriorly, the phrenic nerve is identified and the pleura overlying the superior pulmonary vein is incised. From an inferior to superior direction, the superior pulmonary vein is dissected away from the underlying pulmonary artery. Next the superior aspect of the vein is cleared from the pulmonary artery by removing the anterior aspect of the station #10L nodal bundle. The superior pulmonary vein is encircled from an inferior to superior direction using the curved tip thoracic grasper. A vessel loop is passed under the vein and the vein is divided with a stapler using a white vascular cartridge [Figure 12].

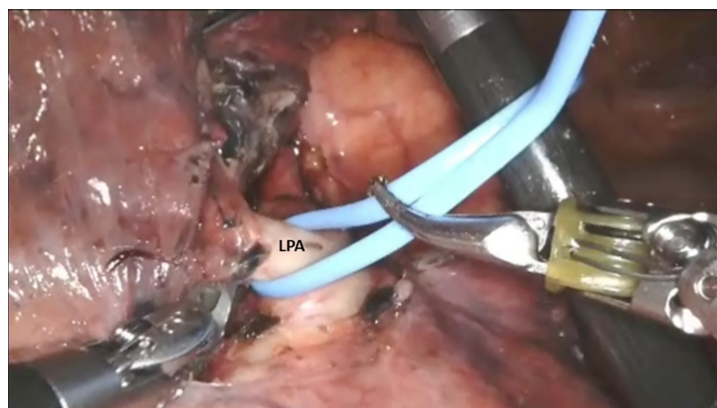


Figure 11. The artery is encircled and elevated with a vessel loop. LPA: lingular pulmonary artery

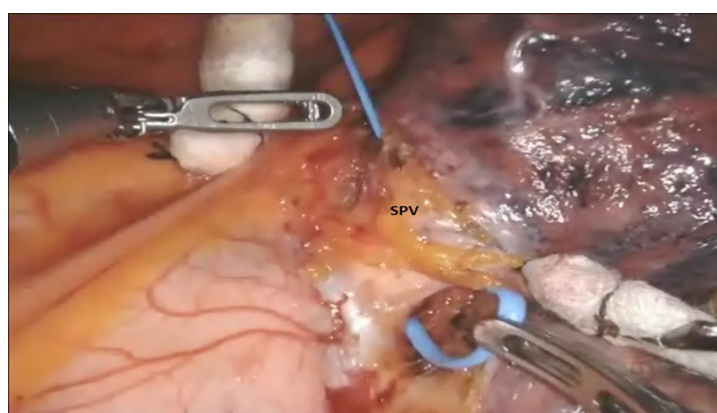


Figure 12. The vessel loop is used to elevate the SPV from the underlying pulmonary artery. SPV: superior pulmonary vein

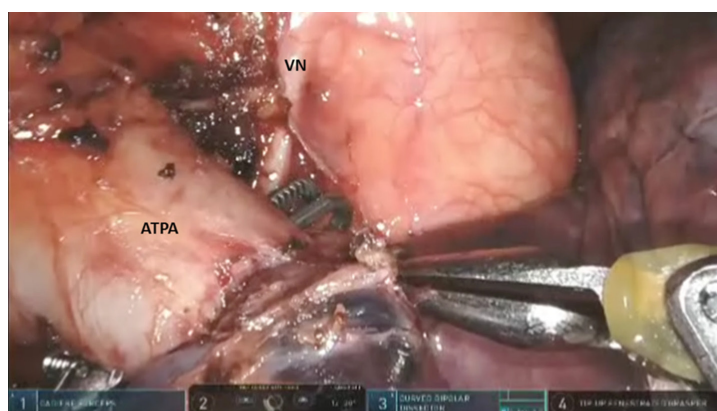


Figure 13. The Cadiere forceps is passed under the ATPA. The VN is seen at the level of the aortic arch. VN: vagus nerve; ATPA: anterior branch of the pulmonary artery

Division of the superior pulmonary vein allows for the approach to the anterior branch of the upper lobe pulmonary artery. The lung is retracted anteriorly. The Cadiere forceps is to pass under the anterior branch of the pulmonary artery, a vessel loop is used to encircle and elevate the artery branch, and it is divided with a stapler with a white vascular cartridge, which is introduced from a medial to lateral direction [Figure 13].

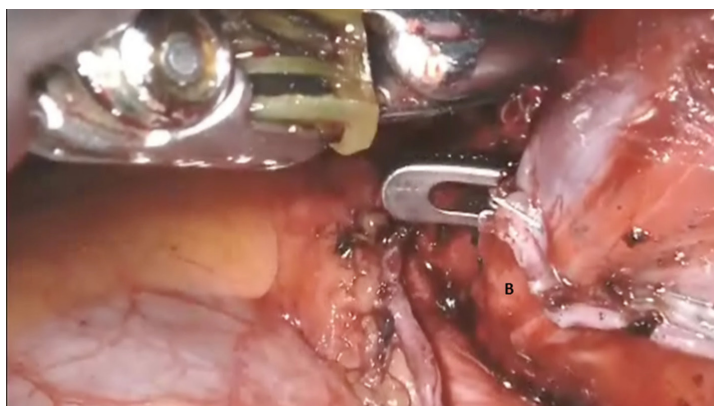


Figure 14. A curved tip forceps is passed from an inferior to superior direction under the left mainstem bronchus (B)

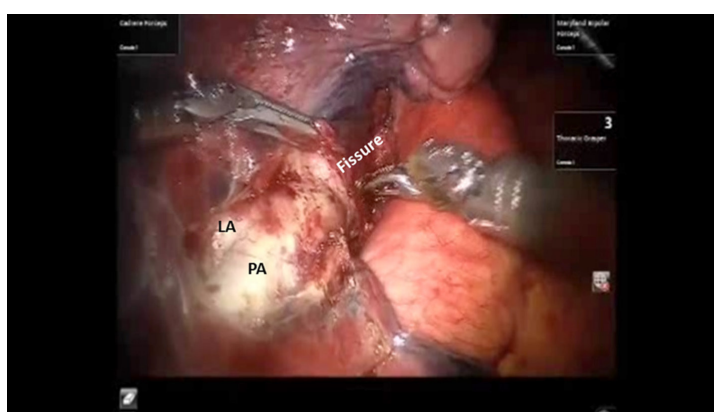


Figure 15. The sub-adventitial plane overlying the PA is entered, and dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure towards the main pulmonary artery. LA: lingular artery; PA: pulmonary artery

The anterior aspect of the oblique fissure is divided from a medial to lateral direction. This maneuver facilitates the identification of the inferior aspect of the lingular bronchus and thereby, the left upper lobe bronchus. The anesthesiologist is asked to remove the intrabronchial suction catheter. The “Curved Tip-Up” thoracic grasper is passed from an inferior to superior direction under the left upper lobe bronchus, a vessel loop is passed around the bronchus and used to elevate the bronchus, and the bronchus is divided using a stapler with a green cartridge which is passed from an inferior to superior direction [Figure 14].

The specimen is placed into the anchor bag and the bag is closed under direct vision ensuring that the entire lobe is inside the bag. The straps are brought out through the access port and used to retrieve the bag containing the lobe.

Left lower lobectomy

Port placement, instruments, and mediastinal nodal dissection are similar to left upper lobectomy.

After mediastinal nodal dissection, the upper lobe and lower lobe are retracted in opposite directions and the fissure is identified. Dissection of the nodal bundle in station #11 allows for identification of the pulmonary artery in the fissure. The artery is most superficial at the junction of the lingula, upper lobe and the lower lobe. The sub-adventitial plane is entered, and dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure towards the main pulmonary artery [Figure 15].

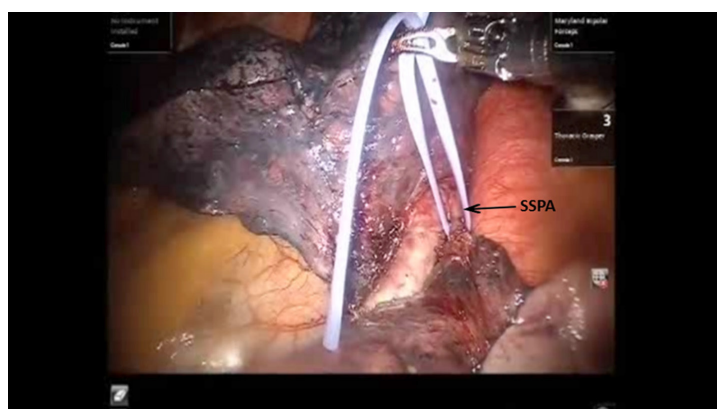


Figure 16. A vessel loop is passed underneath the SSPA and used to encircle and elevate the vessel. SSPA: superior segmental pulmonary artery

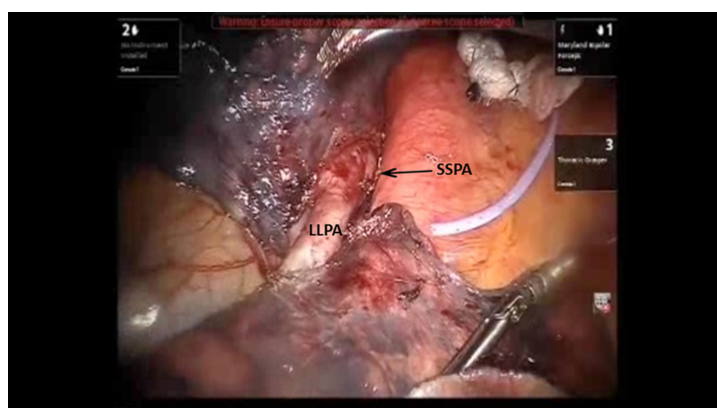


Figure 17. The LLPA is encircled with a vessel loop. Divided end of the SSPA is seen. LLPA: lower lobe pulmonary artery; SSPA: superior segmental pulmonary artery

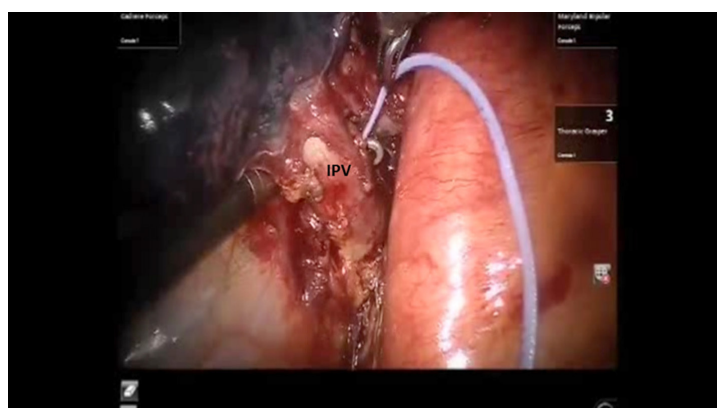


Figure 18. The Cardiere forceps is passed from a medial to lateral direction under the IPV. IPV: inferior pulmonary vein

The Cadere forceps is used to pass a vessel loop under the pulmonary parenchyma in the posterior aspect of the fissure. A stapler with a blue cartridge is used to divide the tissue in the posterior aspect of the fissure. The sub-adventitial plane is then developed anteriorly in order to identify the lower lobe branch of the pulmonary artery. The anterior aspect of the oblique fissure is divided. The superior segmental

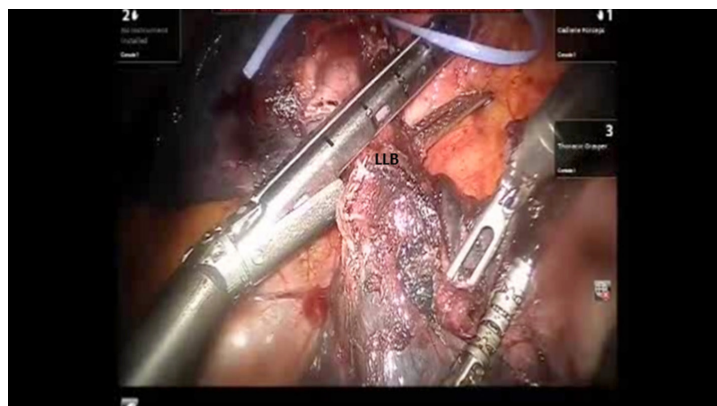


Figure 19. The bronchus to the LLB is divided using a stapler with a purple cartridge. LLB: left lower lobe

pulmonary artery is also identified. The Cadere forceps is passed under the superior segmental pulmonary artery, a vessel loop is passed underneath and used to encircle and elevate the vessel, and the vessel is divided with a stapler with a white vascular cartridge introduced from a medial to lateral direction [Figure 16]. Next, the lower lobe artery is encircled and divided in a similar fashion with a white cartridge [Figure 17].

The lung is elevated and retracted medially. The Cadere forceps is passed from a medial to lateral direction under the inferior pulmonary vein, a vessel loop is used to encircle and elevate the vein. The inferior pulmonary vein is divided using a stapler with a white vascular load introduced from inferior to superior direction [Figure 18].

Finally, the bronchus is divided using a stapler with a purple cartridge [Figure 19]. The lower lobe specimen is removed using the same technique as has been described with the upper lobe.

CONCLUSION

Robotic lobectomy has been evolving over the past decade and has been shown to be an oncologically acceptable procedure. A methodical approach to the conduct of the lobectomies and a proven strategy for the control of major vascular injury will increase adoption.

DECLARATIONS

Authors' contributions

Collected the data, performed the procedures, and composed the manuscript: Gharagozloo F, Meyer M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Technique of robotic lobectomy III: control of major vascular injury, the 5 “P”s

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Abstract

Robotic Lobectomy has been evolving over the past decade and has been shown to be an oncologically efficacious procedure. Although robotic lobectomy is performed more frequently in centers around the world, it accounts for a small percentage of all lobectomies. One of the major causes of reluctance to adopt robotic lobectomy and segmentectomy procedures by surgeons is the fear of bleeding complications, as well as the lack of a standardized reproducible approach to these potentially catastrophic events. This paper outlines a proven strategy for control of bleeding complications during robotic lobectomy and segmentectomy procedures: the 5 “P”s of Prevention, Preparedness, Poise, Pressure, and Proximal Control.

Keywords: Robotic, lobectomy, bleeding, upper lobectomy, middle lobectomy, lower lobectomy, lobectomy, conversion, lung cancer, 5 “P”s

INTRODUCTION

Although robotic lobectomy is performed more frequently in centers around the world, it accounts for a small percentage of all lobectomies. One of the determinants for the lower level of adoption of the robotic lobectomy and segmentectomy procedures is concern about catastrophic bleeding complications, as well as a reproducible strategy for the control of bleeding.



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The overall incidence of major vascular injury during elective robotic thoracic operations was reported to be 1.2% (16 of 1,304 operations) by Cerfolio *et al.*^[1]. These authors reported the incidence of major vascular injury during robotic lobectomy as 2.6% and for robotic segmentectomy as 1.5%. Novellis *et al.*^[2] reported an overall conversion rate of 6.2% (21/338) for major robotic lung resections, of which 1.1% (4/338) were due to bleeding. Other authors have reported overall conversion rates of 1.5%-9% with pulmonary artery or pulmonary vein injury resulting in conversion in 0.5%-2.6%^[3-7]. In a retrospective multi-institutional study of 1,810 patients who underwent robotic anatomic pulmonary resections, Cao *et al.*^[4] reported intraoperative catastrophic events in 1.9% of patients. Catastrophic events were associated with higher proportion of patients who underwent preoperative radiotherapy, higher perioperative mortality, longer operative times, and higher estimated blood loss. In this study, intraoperative hemorrhage from the pulmonary artery was the most common catastrophic event.

Gharagozloo *et al.*^[3] reported their experience with 638 consecutive robotic lobectomies for early stage lung cancer. Conversion to a thoracotomy occurred in 11 (1.7%) patients. Six of eleven (54%) conversions were for bleeding (0.9% of robotic lobectomies).

The most common intraoperative bleeding complication during robotic lung resection is from an injury to the pulmonary artery. Most commonly, pulmonary artery injury occurs during dissection of the artery^[4]. These injuries are easier to see as they occur directly at the point of dissection. Injury to the pulmonary artery can also occur at the time of encirclement of the artery branch and passage of the stapling device^[5,6]. In these instances, the pulmonary artery is usually torn at the branch point resulting in a more central injury. Most commonly, a central pulmonary artery injury occurs during left upper lobectomy and is associated with dissection, isolation, and division of the truncus branch. The risk factors for pulmonary artery injury with robotic lung resection are similar to open or conventional video-assisted (VATS) procedures. The risk of pulmonary artery injury is increased in patients who have received induction chemo- and/or radiation therapy, have larger tumors, and in the presence of calcified lymph nodes^[6-8].

Pulmonary vein injury is much less common than pulmonary arterial injury^[4]. Pulmonary vein injuries can be more easily repaired using minimally invasive techniques such as stapling or over sewing. The most important technical aspect of managing a pulmonary vein injury is to prevent air embolism by resisting vigorous suction at the bleeding point. Control of the pulmonary vein bleeding by “pressure” is preferred and is similar to what is outlined for the artery below.

This paper outlines a proven strategy for control of bleeding complications during robotic lung resections.

Strategy for the Control of Major Vascular Injury: Cerfolio *et al.*^[1] described the 4 “P”s as the technique for the control of major vascular injury: Poise, Pressure, Preparedness, and Proximal Control. Preparedness can be further expanded to Prevention of the injury and Preparedness of the team to respond to the catastrophic event.

THE 5 “P”S

Prevention

First and foremost is Prevention. Prevention of major vascular injury dictates a different approach to the dissection of the vascular structures during robotic lung resection. Unlike the technique of open and VATS lobectomy where the artery branches are dissected and divided in a sequential manner, robotic lung surgery requires a wider dissection of the mediastinum, the proximal and distal portions of the artery and vein. The strategy of robotic lung resection starts with a wide mediastinal nodal dissection with identification of the proximal broncho-vascular structures. This is followed by dissection of the smaller vascular branches. As a general rule, the dissection of the smaller vascular branch should only be

undertaken after the more proximal portion of the artery or vein has been fully dissected. This strategy results in less tension on the branch points, ready access to the proximal portion of the artery or vein in the case of injury, and a more controlled approach to the bleeding complication, which, in turns, increases the odds of mitigation of bleeding without resorting to conversion to a thoracotomy. Prevention of major vascular injury requires complete and methodical dissection of the perivascular structures, as outlined in Technique of Robotic Lobectomy I and II. The completion of the mediastinal nodal dissection allows for mobilization of the bronchial and vascular structures. Dissection and removal of perivascular N1 nodes allows for full visualization of the PA branches and allows for a safer approach to the isolation and division of the vessel. The use of vessel loops for elevation of the vascular branch and the use of staplers with guide catheters further decreases the chance of vascular injury. As a rule, the branch of the pulmonary artery and the proximal portion of the artery which gives rise to the branch should be completely dissected before any attempt is made to encircle the branch. Decreasing tension on the branch point is an excellent technique for avoiding injury to the artery. In general, greater dissection leads to safer control of the pulmonary artery branches and prevention of catastrophic bleeding. Furthermore, following these principles facilitates proximal control and control of bleeding in the event of injury to the pulmonary artery. In our view, all the steps of robotic lobectomy should be designed to build a foundation of safety for prevention of vascular injury. The “P” for prevention is the most important of the 5 “P”s.

Preparedness

Anesthesia and the surgical team need to prepare by running drills such that each team member is totally ready for their function in the event of vascular injury. This requires a dedicated anesthesia and nursing team. Thoracotomy trays must be in the room, and possibly opened and counted depending on the experience of the surgeon. Blood needs to be available, dictating the need to routinely type and cross match blood for the patients who undergo robotic lobectomy and segmentectomy.

Poise

Poise is the first and most critical aspect of the response to a catastrophic injury. The primary surgeon must remain as relaxed as possible in order to create a calm and methodical approach to the problem. The primary surgeon needs to impart an attitude of confidence and calmness to all members of the surgical and anesthesia teams. This is only possible when there is a specific anesthesia and OR team, and if the team has prepared for the emergency by running regular disaster readiness drills.

Pressure

By virtue of being a low pressure and high flow vessel, pulmonary artery bleeding can be controlled with pressure. Attempts at grabbing the artery should be discouraged as this maneuver which works best for high pressure vessels will tend to enlarge the tear. The best approach is to have a tightly rolled sponge in the field. In the event of bleeding, the rolled sponge is placed over the bleeding point with the left robotic instrument (usually Cadiere forceps) and pressure is maintained [Figure 1]. Next, the assistant introduces a tightly rolled sponge which is covered with “EVARREST” fibrin sealant patch (Ethicon, Inc. Somerville, NJ, USA) [Figures 2 and 3]. The patch attached to a tightly rolled sponge is grasped by the right robotic instrument (usually a curved bipolar). In a swift motion, the sponge in the left hand is removed and replaced with the sponge carrying the EVERREST patch [Figure 4]. The patch is held over the bleeding point for exactly 3 min. Following this, the patch should be left in place and the fourth arm should be used to continue pressure on the sponge/patch composite. The tendency to assess the state of the tear should be absolutely avoided. The patch should be left in place until proximal control is obtained.

Pulmonary vein injury usually occurs during dissection and encirclement maneuvers. Most commonly, the upper lobe veins are injured. Usually, the injury is on the underside of the vein. In the case of pulmonary vein injury, suction of blood should be avoided as this may lead to air (CO₂) embolism. The bleeding



Figure 1. Injury to the superior segmental pulmonary artery, during left lower lobectomy. A rolled sponge which is always placed in the proximity of the dissection is used to control the bleeding using the right robotic arm. LUL: left upper lobe; LLL: left lower lobe

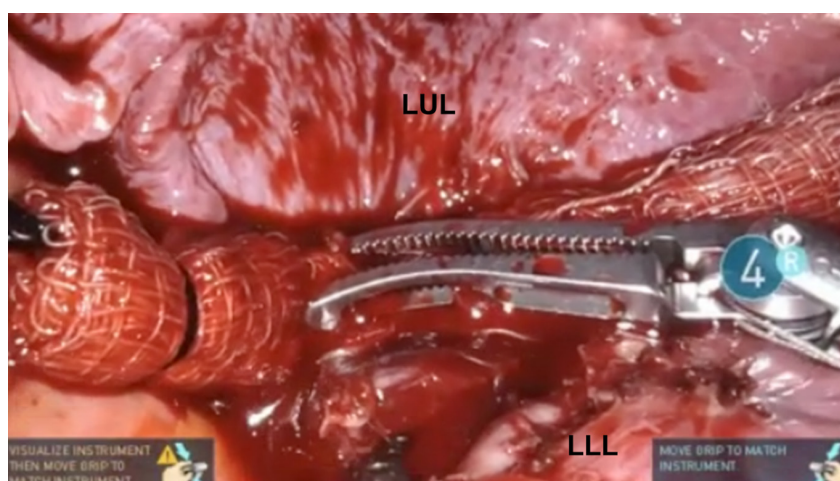


Figure 2. Injury to the superior segmental pulmonary artery, during left lower lobectomy. A rolled sponge which is always placed in the proximity of the dissection is used to control the bleeding using the right robotic arm. The blood is removed by the assistant using suction and the sponge is more accurately placed over the injury. LUL: left upper lobe; LLL: left lower lobe



Figure 3. Rolled sponge and a strip of EVERREST Hemostatic Patch

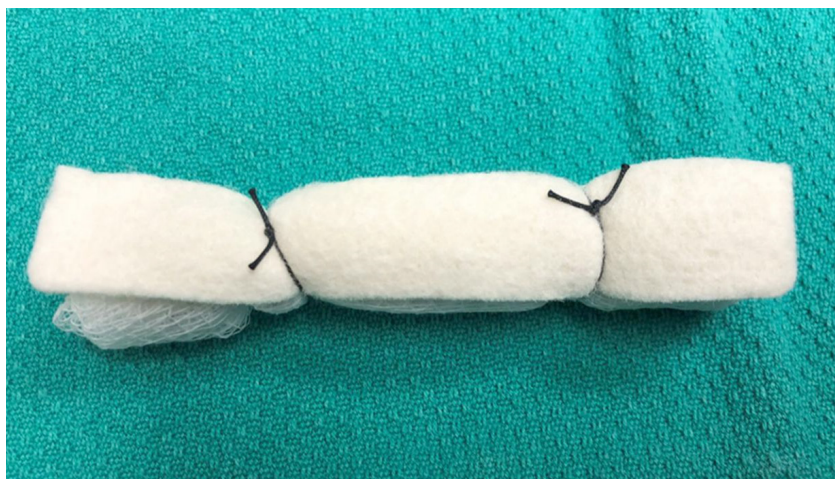


Figure 4. At the first sign of a bleeding complication, the EVERREST Patch is prepared. The strip of EVERREST is tied onto the tightly rolled sponge and introduced through the accessory port by the assistant

should be controlled with pressure technique, as outlined for the pulmonary artery.

It is important to emphasize that the experience of the surgeon with robotic procedures should dictate the next steps following control of the bleeding. For the less experienced surgeons, the safest strategy is to maintain pressure control of the bleeding and calmly convert to a thoracotomy. Using the accessory port, the assistant can introduce a long metal “Yankauer” suction to place direct pressure on the rolled sponge and/or sponge/EVERREST patch. With pressure control of the bleeding point, the robot arms are removed, and the camera is disconnected from the robot arm and introduced freely through the camera port in order to maintain full visualization of the pleural space and to confirm the control of the bleeding under direct vision. The robot is then moved away from the operating table, and the table is unlocked and turned to the normal position for a thoracotomy. The second assistant is tasked with pressure control of the bleeding point while a scrub nurse holds the camera for visual confirmation. Although some surgeons prefer to disconnect the left arm from the robot cart and use it for pressure control, if a second assistant is available, we prefer the suction pressure technique. The posterolateral thoracotomy is performed calmly and under control. The chest is entered through the 5th intercostal space directly over the oblique fissure in order to have full access to the hilum and the proximal pulmonary artery. After the chest is open, the Yankauer suction is replaced with a conventional kittner carrying a rolled sponge and the pressure control is maintained by the second assistant while the surgeon and the first assistant gain proximal control.

Surgeons with greater experience can obtain proximal control and repair the vascular injury by robotic or endoscopic techniques. However, it must be emphasized that conversion to a thoracotomy should be seen as the safest technique and conversion should be performed in a timely fashion and not as a last resort.

Proximal control

Once the vessel is hemostatic, the surgeon should obtain proximal control by passing a vessel loop around the pulmonary artery or vein proximally, double loop around it, and gently pull up to completely stop its blood flow. At this point, the patch sponge composite should be removed. The injury can be seen because the blood flow is stopped, and it can be sewn using 4-0 nonabsorbable suture or stapled if there is room proximally.

In our experience, pulmonary artery injury should be categorized into two groups: Group I, injury to pulmonary artery branch; and Group II, injury to a central portion of the pulmonary artery. In Group I, the bleeding is usually controlled using the EVERREST technique. In these patients, once the bleeding

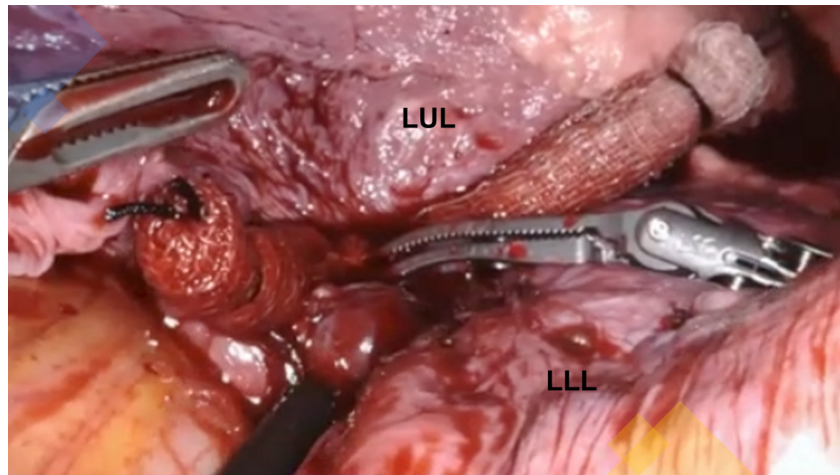


Figure 5. The EVERREST patch is placed over the injury and held in place for 3 min by the clock. LUL: left upper lobe; LLL: left lower lobe

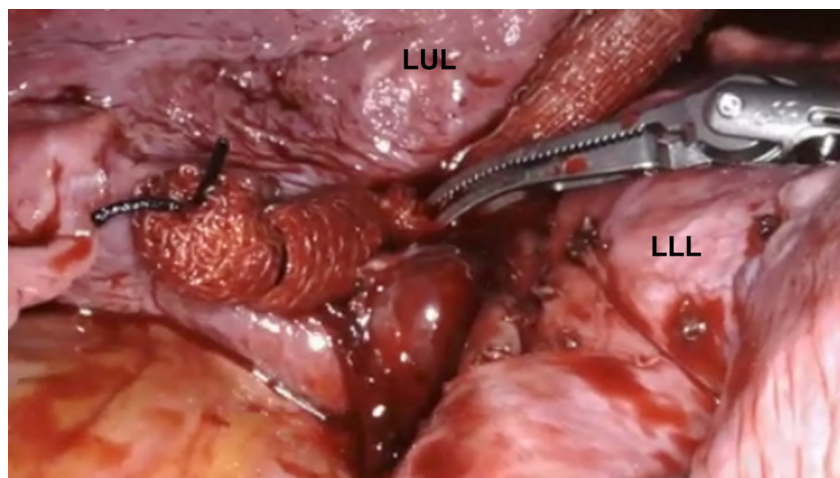


Figure 6. The EVERREST patch is left in place while obtaining proximal control. LUL: left upper lobe; LLL: left lower lobe

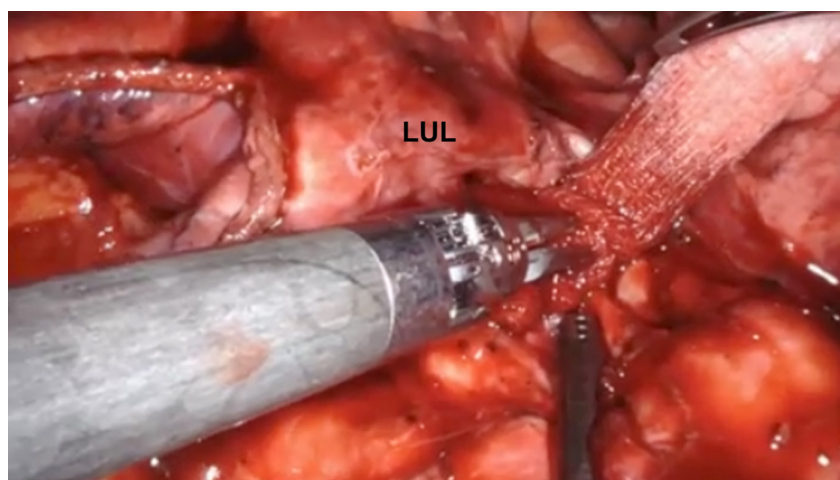


Figure 7. Injury to the proximal pulmonary artery during robotic left upper lobectomy. The rolled sponge with EVERREST patch is used to control the bleeding in preparation for a thoracotomy. LUL: left upper lobe



Figure 8. Closeup view of injury to the proximal pulmonary artery during robotic left upper lobectomy. The rolled sponge with EVERREST patch is used to control the bleeding in preparation for a thoracotomy

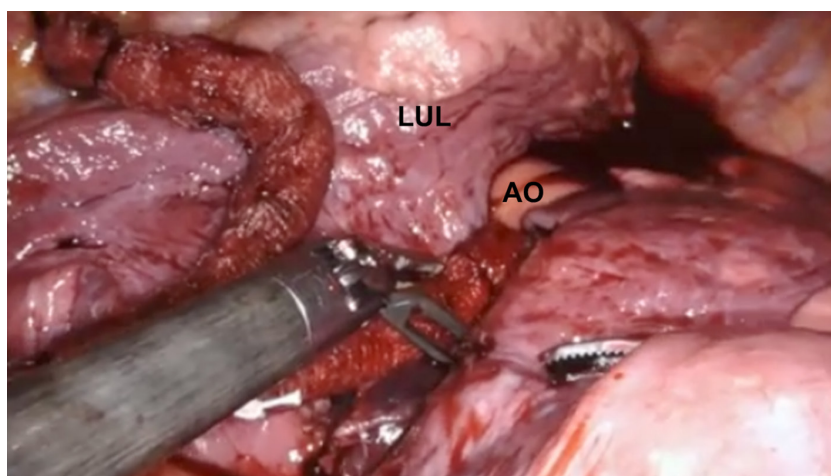


Figure 9. Injury to the proximal pulmonary artery during robotic left upper lobectomy. Due to the inability to obtain direction compression of the injury, the rolled sponge with EVERREST patch is not sufficient for controlling the bleeding. It is used to control the bleeding in preparation for a thoracotomy. LUL: left upper lobe; AO: aortic arch

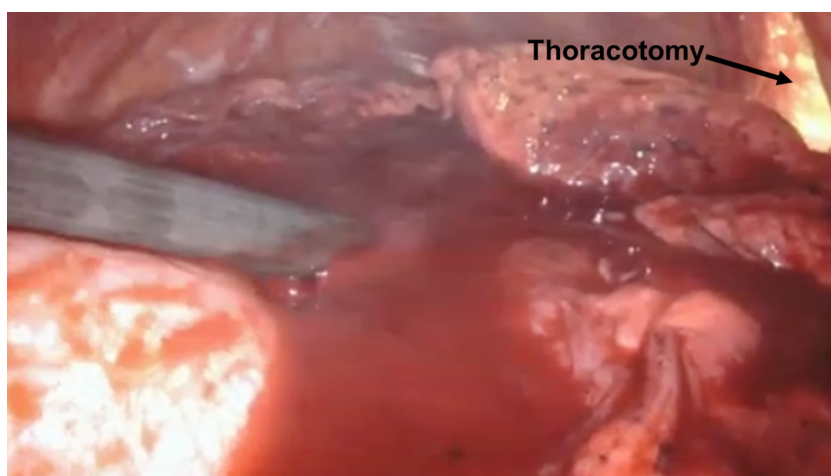


Figure 10. Injury to the proximal pulmonary artery during robotic left upper lobectomy. The robotic arms are removed. Bleeding is controlled by pressure on the EVERREST patch. The assistant introduces a suction introduced through the accessory port, while the surgical team converts to a thoracotomy

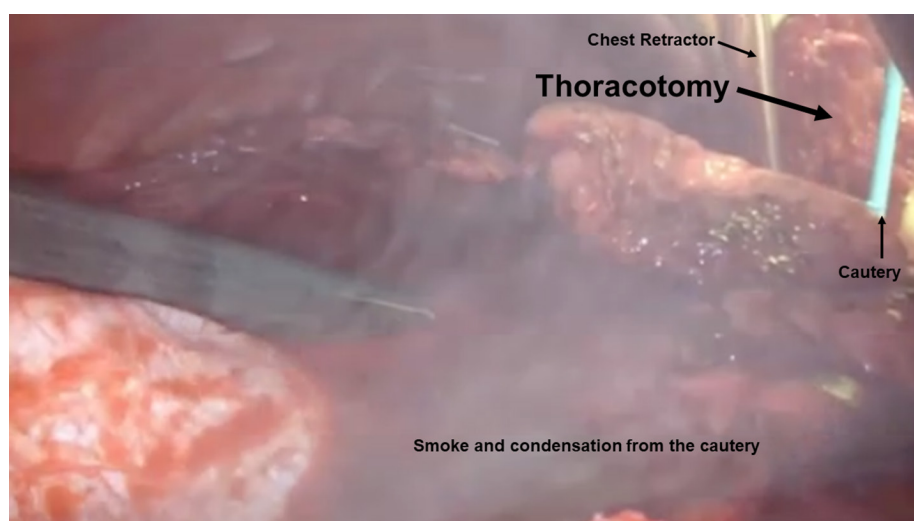


Figure 11. Injury to the proximal pulmonary artery during robotic left upper lobectomy. Thoracotomy is completed in preparation of proximal control and safe repair of the pulmonary artery injury

is controlled, proximal pulmonary artery control is obtained, and bleeding is mitigated using robotic techniques. The most common scenario is to staple the more proximal portion of the pulmonary artery branch [Figures 5 and 6].

In Group II, the injury to the pulmonary artery is more central and requires control of the main pulmonary artery. This group is illustrated by injury to the proximal pulmonary artery during a robotic upper lobectomy procedure. In this group, the EVERREST technique allows for better but not perfect control of the bleeding. In these patients, the pressure needs to be maintained, the robotic procedure needs to be converted to a thoracotomy, and the vascular injury needs to be repaired in a safe manner.

If conversion to thoracotomy is chosen, the robotic instruments need to be completely removed, the robot undocked and moved completely away from the operative field, and the bleeding stopped by the sponges and the pressure maintained on the sponge by an external suction manned by the assistant. Robotic instruments should not be used to hold pressure. In our view, it is best to avoid leaving one arm of the robot in to compress a vessel. It is critical to completely remove the robot from the operative field. If a vessel is still bleeding, pressure needs to be held by means of a nonrobotic instrument through the access port by a bedside assistant while the chest is safely and calmly opened [Figures 7-11].

With greater experience, the minimally invasive technique can be used to control pulmonary artery bleeding. However, until greater experience is gained, and even then, under certain circumstances, an orderly conversion to a thoracotomy should remain the procedure of choice.

CONCLUSION

Intraoperative bleeding complications and catastrophes during pulmonary resection are rare. In fact, due to the uncommon nature of these complications, the surgical team is usually unprepared to manage the catastrophic bleeding and therefore these complications can result in significant consequences for the patient. Robotic surgical teams must have a well-rehearsed reproducible “fire drill” plan so that the team members understand their roles during these uncommon yet potentially catastrophic events. The application of the 5 “P”s to robotic lung resection will increase patient safety and surgeon adoption of these procedures.

DECLARATIONS

Authors' contributions

Collected the data, designed and performed the procedures, and composed the manuscript: Gharagozloo F, Meyer M

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Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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Review

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The Alfieri's edge-to-edge technique for mitral valve repair: from a historical milestone of cardiac surgery to the origin of the transcatheter era

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Abstract

After 30 years since its introduction, the edge-to-edge technique has become one of the most popular and adopted worldwide for surgical repair of mitral regurgitation. The success of this procedure could possibly be explained by its unique simplicity and high level of reproducibility. Indeed, it possesses the ability of being very versatile and it has been used in a wide spectrum of mitral valve pathologies and lesions: from degenerative to functional disease, from posterior to anterior leaflet lesions, including commissural defects. The rapidity of this easy surgical gesture has also enhanced its application in minimally invasive approaches. Finally, it has become a true milestone for the era of transcatheter correction of mitral regurgitation. Here, we describe the history and evolution of this breakthrough in the world of cardiac surgery.

Keywords: Mitral valve repair, edge-to-edge technique, Alfieri's stitch, double-orifice

INTRODUCTION

Mitral valve disease still represents the most frequent valvulopathy^[1]. Several studies have shown the preference of valve repair over replacement due to reduced peri-operative mortality and improved long-term survival, thus becoming the gold standard for treatment of severe degenerative mitral regurgitation (MR)^[2]. At the beginning of the 1980's, Professor Alain Carpentier introduced the so-called "French



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correction”, the first standardized and reproducible toolbox of surgical techniques to treat mitral valve regurgitation^[3]. This approach which is based on the reconstruction of the native valve anatomy mainly through the resection of the prolapsing and excessive tissue, has become a surgical landmark for the art of mitral valve repair, providing optimal long-term outcomes, especially in isolated prolapse of the posterior leaflet^[4]. However, the results of these “anatomical reconstructions” in the setting of anterior, bileaflet and commissural lesions were reported to be less promising^[5].

In 1991, the Italian cardiac surgeon Professor Ottavio Alfieri introduced a surgical technique for the repair of mitral regurgitation, named “edge-to-edge” (later known also as the “Alfieri’s stitch”)^[6]. This revolutionary method was based upon a “functional” rather than “anatomical” conceptualization of the valve repair. In this way, the application of a suture at the site of the regurgitant jet, between the facing free margins of the anterior and posterior leaflets (usually A2 and P2), creates a “double-orifice” valve without residual prolapse of one or both leaflets. Indeed, the most common indication for the edge-to-edge repair is represented by bileaflet prolapse in the setting of Barlow’s, where the excess of myxomatous tissue allows the application of a strong and wide suture, extending along the entire free margins of the central scallops (“central edge-to-edge” or “double orifice repair”). Given the increased risk of systolic anterior motion (SAM) of the anterior mitral leaflet, the iatrogenic fusion of both leaflets by application of the Alfieri’s stitch reduces the fluctuation of the anterior leaflet towards the left ventricular outflow tract (LVOT). On the other hand, the closure of the whole commissural area to treat non-central lesions (“paracommissural edge-to-edge”) preserves the single orifice configuration of the native valve. In addition, the concomitant use of a complete or partial prosthetic ring decreases the tension on the edge-to-edge suture, allowing for further stabilization of the annulus and enhances the overall durability of the repair.

Simplicity and reproducibility represent the main reasons for the success of the Alfieri’s stitch, a truly versatile surgical technique which has been adopted in thousands of patients^[7-13]. This paves way for a breakthrough in the world of cardiac surgery, particularly in percutaneous mitral valve repair^[14].

In this review we will briefly discuss the history of the edge-to-edge mitral valve repair, beginning from its origins, through the initial criticisms, reasons for success, to its ultimate percutaneous evolution.

INDICATIONS FOR MITRAL SURGERY

As stated by the 2017 ESC guidelines on the treatment of valvular heart disease, surgery (especially repair whenever possible) is indicated in cases of severe symptomatic primary mitral valve regurgitation with left ventricle ejection fraction $> 30\%$ ^[2]. In addition, in asymptomatic patients, the presence of Left Ventricle Ejection Fraction (LVEF) $\leq 60\%$ or Left Ventricle End Systolic Diameter ≥ 45 mm, atrial fibrillation or a systolic pulmonary pressure ≥ 50 mmHg predict a worse outcome and therefore surgery should be considered as well. Whenever long durability is predicted, early repair is encouraged.

Severe secondary mitral regurgitation in patients undergoing CABG with LVEF $> 30\%$ is another indication for surgery (class I; level C). However, when LVEF is $< 30\%$ but the patient still has an option for revascularization and there is evidence of myocardial viability, surgery should be considered (class IIa; level C). If revascularization is not indicated, surgery may be considered in those patients who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk (class IIb; level C).

Compared to replacement, surgical mitral valve (MV) repair has shown optimal early-, mid- and long-term results, with a lower peri-operative mortality rate^[15]. In experienced centers, at 20 years, the reported MR recurrence rate after repair is around 10% ^[16]. On the other hand, repair for secondary MR has shown to be less durable, with a significant rate of recurrence at 2 years^[17]. The presence of echocardiographic

factors indicating an increased mitral valve deformation (such as coaptation distance ≥ 1 cm; tenting area $> 2.5\text{-}3\text{ cm}^2$; complex jets *etc.*) or a high level of local and global LV remodeling account for an unfavorable repair^[18].

In the presence of relevant comorbidities and high surgical risk, a percutaneous edge-to-edge procedure may be considered in patients with primary or secondary MR, who remain symptomatic despite optimal medical therapy (including CRT if indicated), with echocardiographic screening required for perioperative risk stratification and assessment of suitability (class IIB; level C). The Heart Team may consider this transcatheter option after careful evaluation of other strategies (i.e., left ventricular assistant devices or heart transplant).

THE IDEA

At the beginning of the 90's, a young woman who suffered from symptomatic severe mitral valve regurgitation asked Professor Alfieri's to perform her own surgery. However, despite a comprehensible feeling of anxiety and fear of the intervention, another reason justified her melanchony: the unlikelihood of having a pregnancy after surgery. Indeed, her anterior mitral leaflet lesion appeared to be not suitable for a conventional repair. Alternatively, the durability of a bioprosthesis would have been very poor and a mechanical prosthesis would have dramatically increase the risks of a potential pregnancy. It was in this scenario that Professor Alfieri, particularly impressed by the aspiration of the young lady to become a mother, had the intuition of anchoring the prolapsing scallop of the anterior leaflet to the facing segment of the posterior leaflet, which had normal mobility. This concept of a valve with a double-orifice was derived from the world of congenital diseases. Previously, he had occasionally observed that patients with a congenital double-orifice valve rarely had a pathological evolution in regurgitation. In other words, the double-orifice design, derived from "a congenital mistake", would have become now a simple solution to fix complex anatomical mitral valve lesions. Despite the uncertainties of a new surgical procedure, Professor Alfieri obtained the informed consent from the patient and an efficient mitral valve repair was achieved with the novel "Alfieri's Edge-to-Edge" technique. A few years later, the patient gave birth to three healthy children.

THE SURGICAL TECHNIQUE

Usually, the "double orifice" repair starts with the inspection of the valve and the analysis of the target lesion (see next paragraph). Once the indication for the adoption of the edge-to-edge technique has been identified, the proper repair begins. After identification of the central portion of the valve, the edge-to-edge suture (generally 4-0 polypropylene) is placed exactly in the middle of the leaflet and, then, a mattress followed by a running suture is extended on both sides (antero-lateral and postero-medial), to cover the regurgitant jet site [Figure 1]. The injection of saline solution helps to test the hydrodynamic competence of the repaired valve. The resulting double-orifice valve area can be directly measured by Hegar dilators (at least 2.5 cm^2 for a normal size patient) and assessed by intra-operative trans-oesophageal echocardiography (TOE).

Moreover, the application of a complete or a partial prosthetic ring prevents further annular dilatation. In addition, it helps in reducing the stress on the edge-to-edge thus preserving long-term durability of the repair. Indeed, it has been demonstrated that the absence of an annuloplasty ring is associated with higher repair failure: in a series of 260 patients undergoing edge-to-edge repair, 52 of them did not received an annuloplasty for severe annular calcification ($n = 44$) or absence of annular dilatation ($n = 8$). The 5-years freedom from reoperation was 92% and 70% in those who annuloplasty was performed or not, respectively^[19]. Similarly, in a series of 61 patients treated with the Alfieri's technique at the beginning of the experience without annuloplasty, the long-term results were not satisfactory: the 12-years the freedom from recurrence of moderate-to-severe MR was 43% and the freedom from reoperation was 58%^[20].

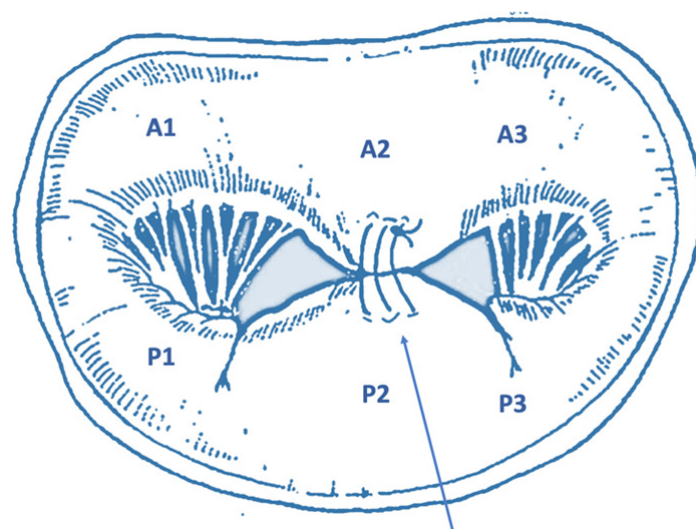


Figure 1. Central edge-to-edge. Schematic representation of the application of the Alfieri's repair applied in the central portion of the mitral valve (A2-P2), originating an artificial double-orifice valve

The introduction of a double-orifice valve, however, has been debated for a long time since it dramatically changes the valve shape and the previous historical concept of the “French correction”, by which native valve anatomy should be restored. However, the ability of subsequent computational models to detect that the hemodynamic performance of a double-orifice valve mainly depends on the whole valve area and cardiac output, rather than on the presence of one or two orifices. In this setting, the flow velocity through each orifice corresponds to that of a single orifice with an area which is the sum of the two. It can happen that the prolapsing lesion is placed not exactly at the center of the valve but slightly more laterally or medially. In these cases, the edge-to-edge suture will lead to a valve with two orifices of different sizes. Although the area of the two orifices will be different, the Doppler velocity flow will remain the same in both orifices.

One of the main concerns regarding the edge-to-edge repair was the impact that an artificial double-orifice valve configuration would have during exercise, particularly in terms of the risk of mitral stenosis. Numerous studies reported that, under exercise testing, despite a physiological increase in transvalvular gradients, the hemodynamics values do not result in pathologic stenosis (mean gradient from 2.8 ± 1.3 to 4.6 ± 1.9 mmHg at rest and exercise, respectively; $P < 0.0001$)^[21], and do not differ from varying resection techniques^[22].

TARGET LESIONS

Throughout the past decades, the Alfieri repair has shown to be a very versatile technique, since it fits with a variety of target lesions and valve diseases. Here, we present the main indications of the edge-to-edge technique.

Bileaflet lesion

Barlow's disease is generally responsible for lesions involving both leaflets. The presence of redundant myxomatous tissue allows the application of wide and deep edge-to-edge stitches, thus reducing the leaflets' height. In addition, converse to longer procedures targeting the chordal/papillary muscle apparatus, it can be easily and quickly performed, thus reducing ischemic time while still achieving excellent results. The first published data showed a low incidence of perioperative mortality (0.92%; $n = 6/648$) and good middle-term clinical outcome (5-year survival $92\% \pm 4.5\%$; freedom from reoperation $91\% \pm 4.2\%$)^[23]. Long-term results have confirmed excellent durability with no evidence of late mitral stenosis^[24].

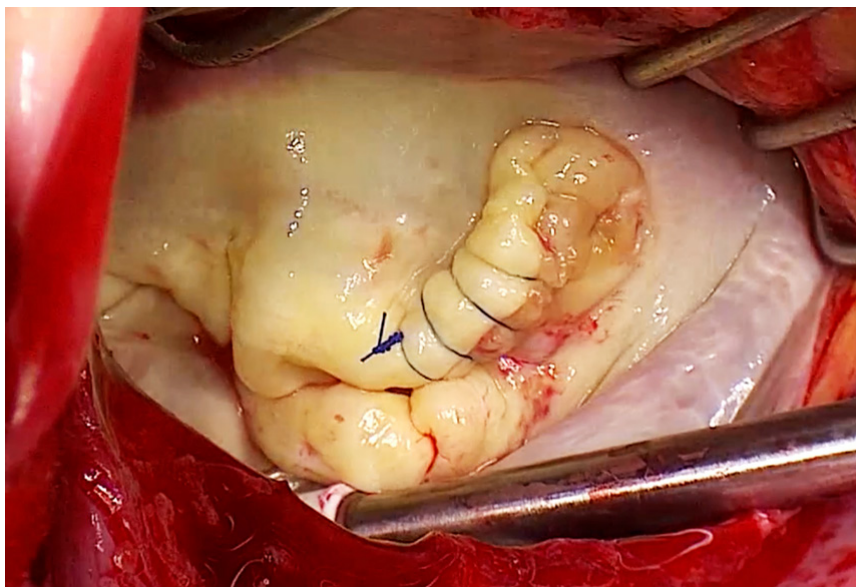


Figure 2. Paracommissural edge-to-edge. Alfieri's technique in a case of a postero-medial commissural prolapse due to previous endocarditis (ring annuloplasty still to be added). In this situation, the configuration of a single-orifice valve is maintained

Anterior leaflet prolapse

When the prolapsing lesion is limited to the central scallop of the anterior leaflet (A2), the edge-to-edge technique provides excellent late outcomes, thus avoiding the need of artificial chordae implantation^[25]. In a series of 139 patients, a 17-year survival rate of $72.4\% \pm 7.89\%$, freedom from cardiac death of $90.8\% \pm 4.77\%$ and freedom from reoperation of $89.6\% \pm 2.74\%$ were reported. Recurrence of MR grade $\geq 3+$ was documented in 12.5% (17/135) of cases. At multivariate analysis, the predictors of MR recurrence include the presence of a greater-than-mild residual MR at discharge (HR: 7.4; 95%CI: 2.5-21.2; $P = 0.001$) and the use of a pericardial rather than a prosthetic ring annuloplasty (HR: 2.8; 95%CI: 0.9-8.7; $P = 0.06$)^[26].

Paracommissural edge-to-edge

Commissural lesions remain very challenging to repair, even for most experienced surgeons [Figure 2]. On the other hand, the application of the edge-to-edge technique can fixate the valve in a few minutes. Indeed, results in 115 patients treated with paracommissural edge-to-edge technique combined with annuloplasty ring showed a 2-year recurrence of severe MR in only 2 patients (1.9%), again without evidence of mitral stenosis^[27]. Similarly, the Cleveland Clinic reported encouraging data on more than 100 of patients treated with closure of the prolapsing commissure^[28].

Functional mitral valve disease

Mitral regurgitation in the setting of ischemic or non-ischemic dilated cardiomyopathy is secondary to both apical tenting of the leaflets and annular dilatation in remodeled ventricles. In the presence of moderate tethering and a relatively small ventricle, the application of an undersized annuloplasty using a complete rigid or semirigid ring may be an effective solution. When leaflet tethering is more pronounced (coaptation depth > 1 cm), it has been proposed that the association of a central edge-to-edge technique could enhance the durability of the repair. Unfortunately, Bhudia and colleagues showed a 2-year recurrence rate of moderate-to-severe MR post-operatively in secondary MR of 24%^[11]. However, in this series the application of flexible bands was probably not enough to support the annulus and prevent its further dilatation, which was the common finding at reoperations. Better results were described by the Alfieri's group, with a 5-year freedom from repair failure of $95\% \pm 3.4\%$, significantly higher as compared to that of isolated annuloplasty without edge-to-edge ($77\% \pm 12.1\%$; $P = 0.04$)^[29].

Systolic anterior motion

It has been postulated that the edge-to-edge technique may play a role in the prevention of post-repair SAM of the anterior mitral valve leaflet, which can dynamically create LVOT obstruction in the presence of anatomical risk factors. Few series reported such results of the edge-to-edge in this setting, and even less in the context of hypertrophic obstructive cardiomyopathy (HOCM). Mascagni and coworkers adopted the double-orifice technique to treat successfully four patients with post-repair SAM^[30], while Brinster *et al.*^[12] showed optimal results in 20 cases even at 4 years of follow-up without the need for reintervention. In our center, we adopted the edge-to-edge technique to treat 26 HOCM patients in which septal thickness was considered inadequate to allow for a safe and effective myectomy with good outcomes: the 8-year cumulative incidence function (CIF) of reoperation with death as a competing risk was $7.7\% \pm 5.2\%$ ^[31].

Rescue edge-to-edge

The double-orifice technique, due to the intrinsic versatility and rapidity of its surgical gesture, which is not time-consuming, has proved to be a valid option even as a rescue procedure, which means to improve the initial suboptimal result of a conventional repair, when the attempt to save the valve becomes a “surgeon’s nightmare”. Gatti *et al.*^[32] described this strategy in 11 patients who underwent other repair techniques and a concomitant final rescue edge-to-edge for residual MR, thus reducing the jet area from $3.0 \pm 0.8 \text{ cm}^2$ to $0.7 \pm 0.9 \text{ cm}^2$ ($P = 0.00014$), and adding only $14.9 \pm 2.8 \text{ min}$ to the aortic cross-clamp times. Our experience has been very gratifying under those circumstances^[33]. However, in these challenging scenarios, the efficacy of the edge-to-edge technique may be very difficult to predict, and not surprisingly other authors have reported suboptimal results^[34]. Finally, particular attention should be given when applying an additional edge-to-edge to a triangular/quadrangular resection: the relative reduction of tissue due to previous resection can be responsible for small final orifices, eventually resulting in mitral stenosis, particularly in cases of wide and deep Alfieri’s stitches.

MINIMALLY INVASIVE APPROACH

The edge-to-edge technique can be easily performed through a minimally invasive approach with relatively short the cross-clamp times, which are generally longer in case of small access and limited surgical view as compared to median sternotomy. An antero-lateral right mini-thoracotomy (6 cm) is usually performed through the third or fourth intercostal space and a soft tissue retractor is inserted. After surgical TOE-guided femoral venous and arterial cannulation, cardiopulmonary bypass is instituted at $28\text{--}30^\circ\text{C}$. In those patients who require concomitant procedures, such as atrial septal defect closure or tricuspid valve repair, an additional percutaneous cannula may be inserted in the jugular vein. Endoaortic balloon (Heartport, Inc, Redwood City, CA, USA) inserted in the femoral artery under echocardiographic guidance or transthoracic surgical clamps (i.e., the Chitwood clamp, Scanlan International, Inc, Minneapolis, MN, USA; or the Cygnet flexible clamp, Vitalitec, Plymouth, MA, USA) are adopted for aortic cross-clamp. Antegrade intermittent cold blood cardioplegia or crystalloid cardioplegic solutions are administered directly into the aortic root. Access to the mitral valve is generally achieved through a left atriotomy and a left atrial retractor is placed through a parasternal incision. The valve analysis and repair is performed both under direct and video-assisted vision using a 30° camera.

A robotic approach has been reported as well, since the versatility and simplicity of the double-orifice technique enhances its application^[35].

A recent publication showed excellent long-term results (up to 19 years) with minimally invasive edge-to-edge repair in myxomatous degenerative mitral valve regurgitation^[36]. Indeed, analyzing 97 consecutive patients with severe myxomatous mitral regurgitation who underwent mitral valve repair through a right minithoracotomy between 1999 and 2006, it was reported a 16-year overall survival of $95.9\% \pm 2.02\%$ (95%CI: 89.39–98.43). At 16 years, the CIF of cardiac death, with non-cardiac death as a competing risk,

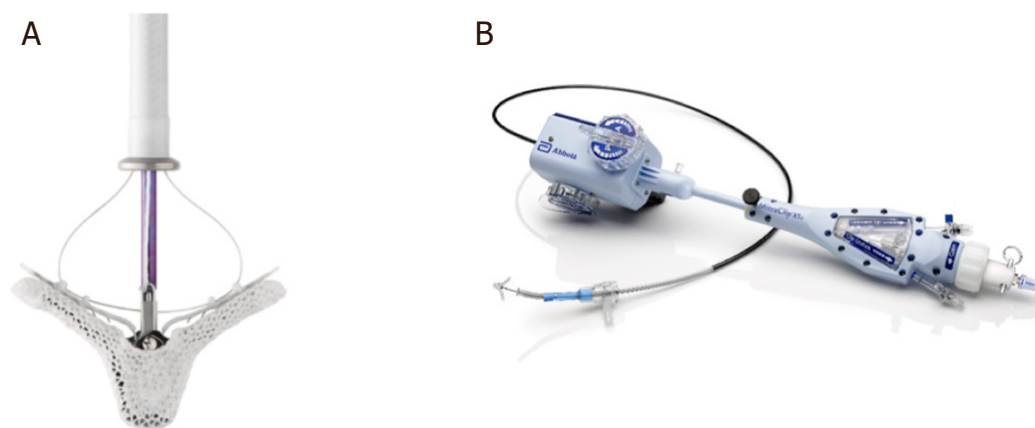


Figure 3. The MitraClip system. On the left, the MitraClip structure with two arms, now 5 mm longer in the XTR version, and grippers (A); on the right the 24 Fr delivery steerable guiding catheter (B) (Courtesy of Abbott)

was 3.1 ± 1.75 (95%CI: 0.83-8.02). Only 4 patients (4.1%) were reoperated for recurrent severe mitral regurgitation (MR). At 16 years, CIF of reoperation and recurrence of MR $\geq 3+$ with death as a competing risk were $3.1\% \pm 1.76\%$ (95%CI: 0.83-8.02) and $5.6\% \pm 2.47\%$ (95%CI: 2.06-11.83) respectively.

It is of pivotal importance that the long-term outcomes are excellent in patients with degenerative MV disease, because current guidelines recommend early repair for asymptomatic patients with severe MR, whenever long durability is predicted^[2]. Providing the patients with the option of a cosmetically favorable procedure without sacrificing efficacy and long-term durability, will facilitate early surgical correction of MR before the development of LV dysfunction. Indeed, most of the target population for this approach will face a long life-expectancy (the mean age of the series previously reported was 35 ± 9 years).

THE ORIGIN OF TRANSCATHETER MITRAL VALVE REPAIR

Simplicity of the edge-to-edge technique enables the possibility of it being translated into a percutaneous approach and constitutes a milestone in the field of cardiovascular medicine, thus paving the way to an era of transcatheter mitral valve repair^[37].

Indeed, the Alfieri's stitch has inspired the development of percutaneous leaflet repair devices such as the MitraClip and the PASCAL systems.

The MitraClip system (Abbott, Chicago, IL, USA) was the first device designed to simulate the surgical edge-to-edge repair. Designed by the Californian start-up Evalve Inc. (purchased by Abbott in 2009), the MitraClip device [Figure 3] was first implanted in 2003^[38]. It has obtained CE mark and FDA approval for treatment of primary MR in 2008 and 2013, respectively. Nowadays, more than 100,000 patients have been treated with the Abbott MitraClip device. After the feasibility study (EVEREST I trial), in 2011 the EVEREST II randomized clinical trial (Endovascular Valve Edge-to-edge REpair Study II trial) reported the outcome of MitraClip compared to surgery in a 2:1 ratio^[39]. A total of 279 patients suffering of moderate-to-severe or severe MR, both degenerative and functional and with a jet originating from malcoaptation of the A2-P2 scallops, were enrolled. Despite the fact that the transcatheter repair showed less efficacy to reduce MR-grade at 1-year, it was found to be superior in terms of safety (major adverse events: 15% clip vs. 48% surgery; $P < 0.001$, almost exclusively driven by difference in blood transfusion) and demonstrated similar clinical outcome improvements (primary composite endpoint were 55% and 73% for the percutaneous edge-to-edge and surgical option, respectively; $P = 0.007$). The 5-year follow-up revealed persistence of a significant difference between groups when considering the primary endpoint (44% vs. 64%

for percutaneous and surgical treatment, respectively; $P = 0.01$), especially when residual MR (12.3% vs. 1.8%; $P = 0.02$) and reoperation (27.9% vs. 8.9%; $P = 0.003$) rates were examined^[40]. However, the need for surgery after the index procedure occurred mainly in the first 6 months of follow-up (78%) and mortality rates did not differ significantly at 5 years (20.8% vs. 26.8%; $P = 0.4$). Unfortunately, it must be stated that the MitraClip cases included in this study were performed at the very beginning of the experience with this new percutaneous approach, thus the learning curve may have played a pivotal role affecting the outcomes reported.

In addition, the small amount of secondary MR patients reported in this study and the enrollment of operable patients only did not reflect the real-world scenario. Two registries, the ACCESS-EU in Northern Europe and the REALISM in United States, enrolled older patients with more comorbidities, mostly with ischemic MR and depressed LVEF^[41]. More recently, two large randomized clinical trials analyzed specifically patients with secondary MR: the MITRA-FR and the COAPT trials. Despite randomization, these studies are still strongly debated by the scientific community for their contrasting outcomes. First, the MITRA-FR study enrolled severe symptomatic secondary MR patients (defined as effective regurgitant orifice area of $> 20 \text{ mm}^2$ or a regurgitant volume of $> 30 \text{ mL}$ per beat) with LV dysfunction (LVEF between 15% and 40%). After 1:1 randomization to medical therapy alone or medical therapy associated to percutaneous edge-to-edge repair, no difference was found in the primary composite outcome of any-cause death or unplanned hospitalization for heart failure at 1 year (55% vs. 51% for the intervention and the control group, respectively; OR: 1.16; 95%CI: 0.73-1.84; $P = 0.53$)^[42].

Conversely, the COAPT trial showed opposite results. In this study 614 severe symptomatic secondary MR patients were 1:1 randomized to maximal doses of guideline-directed medical therapy vs. Mitraclip plus medical treatment^[43]. Both primary and secondary endpoints at 24 months favored the MitraClip cohort, with a hospitalization rate for heart failure of 36% vs. 68% per patient-year (HR: 0.53; 95%CI: 0.40-0.70; $P < 0.001$) and any-cause death rate of 29% vs. 46% for device and control group, respectively (HR: 0.62; 95%CI: 0.46-0.82; $P < 0.001$).

Nevertheless, the contrasting results of these two trials can at least in part be explained by analyzing the major differences between them. The number of clips implanted per-patient was higher in the COAPT, which may justify the lower 1-year rate of severe residual MR as compared to MITRA-FR (5% vs. 17%, respectively). In addition, the COAPT Trial used the definition of ischemic MR severity according to the American Guidelines, resulting in more severe MR at baseline as compared to the MITRA-FR study, which enrolled the patients according to the European Guidelines (mean EROA 31 mm^2 vs. 41 mm^2). Furthermore, indexed left ventricular end-diastolic volumes were larger in the MITRA-FR trial ($135 \pm 35 \text{ mL/m}^2$ vs. $101 \pm 34 \text{ mL/m}^2$). Generally speaking, it seems that patients with more severe secondary MR and not very advanced LV remodeling/dysfunction, may benefit from MR correction/reduction when they remain symptomatic despite optimal guideline-directed medical therapy. Careful selection of the candidates to MitraClip therapy is therefore mandatory. As proposed by Grayburn *et al.*^[44], the identification of proportionate or disproportionate MR could help in the decision-making process for the optimal treatment of secondary MR in patients with chronic heart failure and systolic dysfunction. Indeed, according to the Gorlin formula, patients of the MITRA-FR trial appeared to have proportionate MR since the severity of MR was proportionate to the degree of LV dilatation. Contrarily, participants of the COAPT trial had more severe MR (ERO $0.3\text{-}0.4 \text{ cm}^2$) but less dilated LV (Left Ventricle End Diastolic Volume $160\text{-}200 \text{ mL}$), resulting in disproportionate MR. These specific and selected patients with disproportionate MR seemed to respond better to interventions targeting the mitral valve, like MitraClip. Finally, differences in adherence to optimal guideline-directed medical therapy may have played a role too in influencing the different results of these two studies.

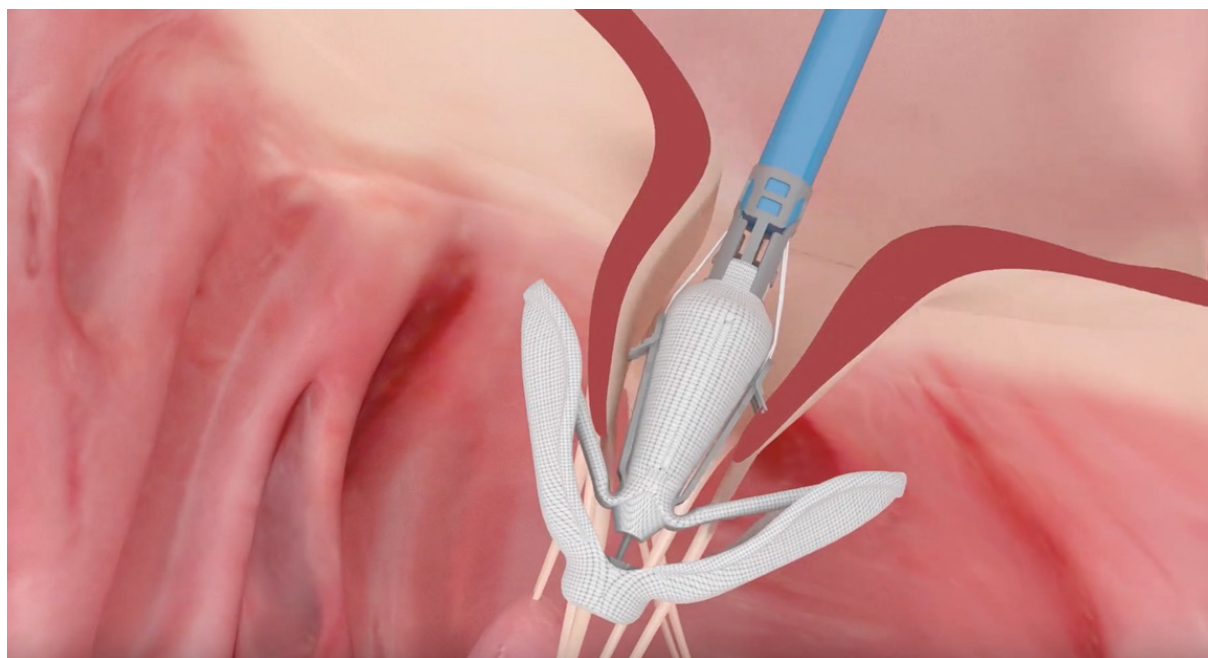


Figure 4. The PASCAL device. The image shows the percutaneous edge-to-spacer system approximating mitral leaflets (Courtesy of Edwards Lifesciences)

The most recent device developed to replicate the edge-to-edge technique is the PASCAL system (Edwards Lifesciences, Irvine, CA, USA), first implanted in 2016. It has obtained CE mark in early 2019, but it is still awaiting FDA approval. Its name, recalling the French scientist Blais Pascal, is linked to that of Professor Alfieri as well (from “Paddles, Spacer, Clasps, Alfieri”). Despite gross similarity to the MitraClip, it substantially differs from it since the mitral leaflets are approximated to the central spacer by using paddles and the grasping is provided by clasps (with a horizontal rather than vertical alignment). In this way, an “edge-to-spacer” repair can be performed with a lower level of tension on the leaflets [Figure 4]. In addition, the higher degree of steerability provides an enhanced navigation into the left heart, allowing independent grasping. This unique feature could be particularly useful in cases of large gaps and significant tethering.

The first-in-man study reported 23 compassionate cases, showing $MR \leq 2+$ in 97% of patients at discharge^[45]. In 2019, Lim *et al.*^[46] reported the early outcome of 62 patients treated with PASCAL (CLASP study). Among them, 56% suffered of functional, 36% of degenerative and 8% of mixed MR etiologies. At 30 days, 98% of patients showed $MR \leq 2+$, all-cause mortality rate was 1.6% and there was no occurrence of strokes. A significant reduction of New York Heart Association class and improvement in quality of life were reported as well.

CONCLUSION

The introduction of the edge-to-edge technique almost 30 years ago has dramatically changed the world of mitral valve repair, not only from a surgical point of view, but also (and even more) from the percutaneous perspective. This simple and versatile surgical gesture has been adopted in a variety of pathologies on thousands of patients. It has also laid the foundations for the percutaneous correction of mitral regurgitation. In other words, it has represented a true milestone in the history of cardiac surgery and, probably, it will keep playing a pivotal role in the future of technological innovations.

DECLARATIONS

Authors' contributions

Drafted the manuscript: Belluschi I, Buzzatti N

Made substantial contributions in conceptualization and revision of the manuscript: Castiglioni C, Alfieri O, De Bonis M

Availability of data and materials

Not applicable.

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Conflicts of interest

The mitral valve repair edge-to-edge technique described in this review was introduced by Prof. Ottavio Alfieri who is a Co-author of this manuscript.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Case Report

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Hearing voices and strange noises after sleeve gastrectomy

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Abstract

Patulous eustachian tube (PET) dysfunction is a rare complication of weight loss, which can be easily misdiagnosed. We present a case of PET dysfunction after laparoscopic sleeve gastrectomy. A 36-year-old Caucasian female with Class III morbid obesity (131 kg, BMI 46.6 kg/m²) successfully underwent laparoscopic sleeve gastrectomy. At her postoperative follow-up appointment six months later, her weight dropped to 96 kg and she complained of severe autophony (hearing of self-generated sounds), leading to anxiety and insomnia. She was initially misdiagnosed with a sinus infection by her primary care provider and was started on antibiotics. She was subsequently seen by an otolaryngologist who diagnosed her with PET. Weight loss can be a predisposing factor for PET. Our patient did not notice onset of symptoms of PET until significant weight loss (35 kg, 59.5% EWL).

Keywords: Sleeve gastrectomy, bariatric surgery, patulous eustachian tube dysfunction, otolaryngology, the Ostmann fat pads, autophony

INTRODUCTION

Patulous eustachian tube (PET) can be difficult to identify and treat^[1]. PET was first described by H. Schwartze in 1864^[1]. PET is defined as a eustachian tube remaining persistently open^[2]. Common PET symptoms include autophony, aural fullness, and hearing one's own breathing (aerophony)^[1]. PET may be caused by rapid weight loss and the consequent wasting of adipose tissue that surrounds the cartilaginous part of the ET, the Ostmann fat pads^[2].



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The current literature reveals PET can be a complication of bariatric surgery such as Roux-en-Y-bypass and symptoms onset after 20 kg weight loss^[3]. A prospective cohort study in Brazil also showed association between gastric bypass (Fobi-Capella technique) and PET^[4]. A poster at the Sages 2017 annual meeting described a case of PET after sleeve gastrectomy with subsequent loss of 27.2 kg (EWL 70%), with BMI 37.9 kg/m²^[5]. We present a case of PET after laparoscopic sleeve gastrectomy and symptoms onset after subsequent weight loss of 35 kg (EWL 59.5%), with BMI 46.6 kg/m².

CASE REPORT

A 36-year-old Caucasian female with Class III morbid obesity (131 kg, BMI 46.6 kg/m²) presented to our multidisciplinary accredited bariatric program in April 2018. She successfully underwent laparoscopic sleeve gastrectomy surgery. At her postoperative follow-up appointment six months later, her weight dropped to 96 kg. She had lost 35 kg, EWL 59.5%. She also complained of severe autophony and aural fullness. She started to hear her own voice and different noises leading to anxiety and insomnia. She could hear her breathing when exercising. It began in her right ear and then she started to experience it bilaterally. There was no otalgia, otorrhea, or tenderness. She denied any history of ear infections, ear surgery, or noise exposure. Autophony was temporarily relieved with lowering her head between her knees or forward-bending. Her symptoms were rapidly progressing. She came to see her primary care provider and was initially misdiagnosed with a sinus infection.

She was started on antibiotics and nasal decongestants, which provided no relief. Nevertheless, her symptoms persisted, and she was subsequently seen by an otolaryngologist. At her otolaryngology visit, her otoscopy revealed clear ear canals. Pure tone testing revealed normal hearing, bilaterally. Word Recognition scores were excellent for each ear. Tympanometry revealed normal middle ear pressure and compliance, bilaterally. PET testing was positive for the right ear; changes to the immittance were synchronous with breathing and most pronounced in the occluded-nostril condition [Figure 1]. Normal hearing with evidence of PET was noted for the right ear. She was officially diagnosed with PET. She was offered medical treatment for PET and decided to monitor her symptoms before proceeding with any surgical intervention. She was recommended nonsteroidal anti-inflammatory medications but wanted to avoid them given history of sleeve gastrectomy. She was started on oxymetazoline for five days and advised to discontinue Flonase. She found acupuncture to be helpful to alleviate some of her symptoms.

DISCUSSION

There is no association between what type of bariatric surgery causes PET. Patients can present to their primary care providers with multiple vague symptoms, which can be challenging to diagnose; therefore, a detailed past medical and surgical history is required. Symptoms can vary from autophony, aural fullness, aerophony, foreign body sensation, and tinnitus to severe anxiety and insomnia^[6]. Symptoms can increase in frequency and duration with time and can be exacerbated with exercise. Symptoms can be relieved with posture (placing the head in a dependent position), upper respiratory infection, or ipsilateral internal jugular vein compression^[7].

Certain diseases such as multiple sclerosis, anorexia, or motor neuron disease can be associated with PET. It is important to consider all the possible differentials including psychiatric illnesses. Stress and anxiety were identified as novel risk factors and may heighten the awareness of internal auditory sounds. According to the literature, auditory verbal hallucinations or hearing voices (multiple voices or sounds such as whispering or murmuring) are the most common symptoms, particularly in schizophrenia^[8].

Our patient was appropriately referred to otolaryngology and diagnosed with PET. Treatment options for PET can be minimally invasive, medical, and surgical depending on the severity of symptoms^[2]. Medical

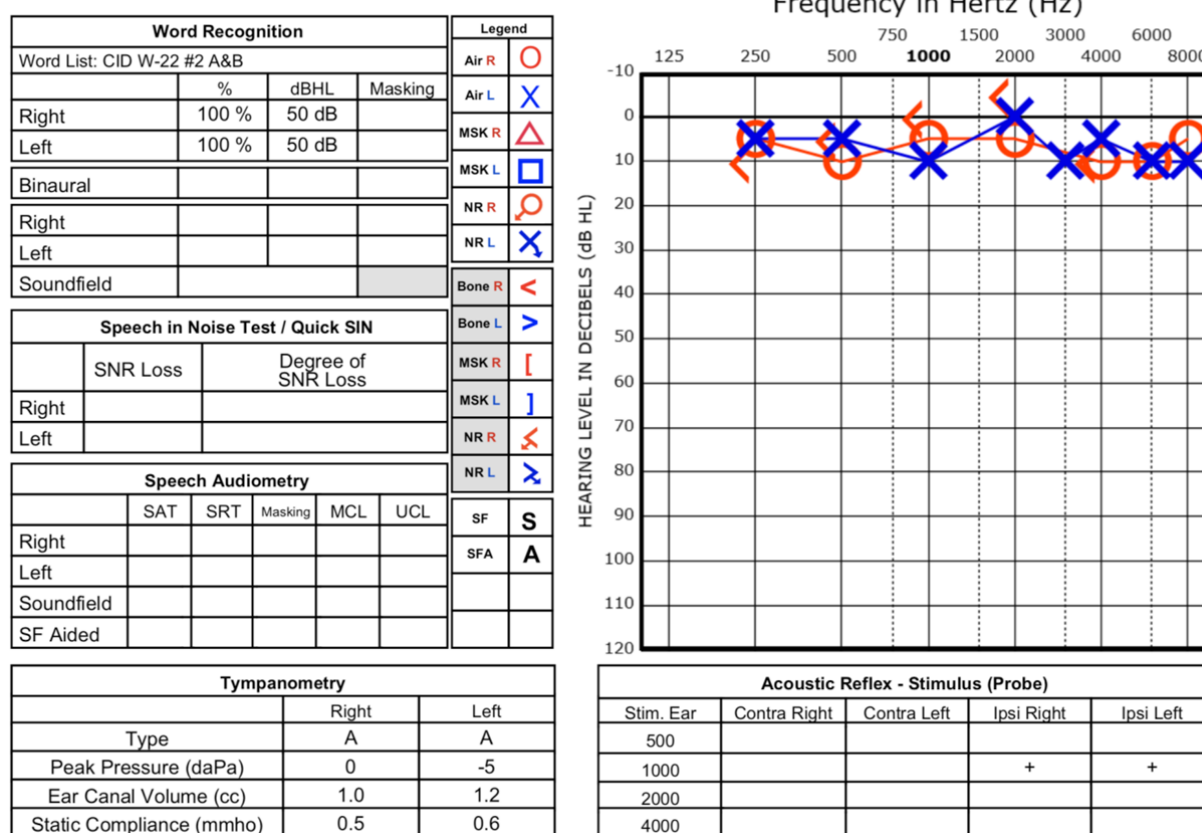


Figure 1. Our patient's audiogram. SF: sound field; SAT: speech awareness threshold; SRT: speech reception threshold; MCL: most comfortable level; UCL: uncomfortable level; SIN: speech-in-noise; SNR: signal-to-noise ratio; SFA: sound-field audiometry; Air: auditory late response; NR: no response

options and minimally invasive options include topical estrogen or insufflation with salicylic or boric acid into the ET pharyngeal orifice. Adequate hydration, nasal saline drops, and saline irrigations can be effective options for symptom management. Decongestants or nasal steroids can, on the contrary, worsen the symptoms. Surgical options are reserved for patients with severe symptoms and include tympanostomy tube insertion, ligation of the orifice, intraluminal catheter placement, cartilage grafting, complete occlusion of the ET, and hamulotomy^[1,9]. It remains unclear whether weight gain can contribute to symptom improvement. Further research is needed to explore the advantages of current treatment options.

Intensity of PET symptoms might vary^[10]. Our patient's symptoms are currently intermittent and tolerable. She did find saline nasal irrigations to be helpful to relieve her symptoms. Our patient continues to lose weight and denies any worsening of her symptoms. It would be helpful to continue to evaluate the severity of symptoms in regards to her weight. PET may be triggered by significant weight loss after sleeve gastrectomy. Raising awareness of the possibility to develop PET after bariatric surgeries would facilitate the right diagnosis and allow appropriate referral and disease management.

DECLARATIONS

Authors' contributions

Manuscript writing: Larionova E

Final approval of manuscript: Jalisi SM, Jones DB

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

We obtained the patient's consent for publication of the present literature.

Consent for publication

Not applicable.

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Review

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The role of endoscopy and radiosurgery in the management of cavernous sinus meningiomas

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Abstract

Cavernous sinus (CS) meningiomas represent a formidable neurosurgical pathology. The desired treatment depends on tumor size and extensions apart from the presenting clinical symptoms of the patient. The last few decades have shown a paradigm shift in the management towards a multimodal treatment. For patients with tumors presenting with a medial extension or when the meningioma occupies the antero-inferior portion of the CS, an endoscopic biopsy can be safely performed through the endonasal route. The boundaries of endoscopic endonasal approaches have been pushed during the last decade, and a direct access to the CS may now be performed. At the same time, an extensive bony decompression to decompress the optic canal and the pituitary gland may be performed. Autologous fat may be interposed between the residual tumor and radiosensitive structures to safely perform adjuvant radiation therapy. The aim of this manuscript is to describe the role of endoscopic surgery in the management of cavernous sinus meningiomas along with the complementary role of radiotherapy. We describe the endoscopic anatomy and the surgical technique to safely perform the procedure and we review the surgical series reported in the literature dealing with the endoscopic approach for CS meningiomas with or without complementary radiation therapy. Endoscopic endonasal approaches have shown promising results in terms of improvement or stabilization of cranial neuropathy and hypopituitarism. Furthermore, the endoscopic approach may enhance the efficacy and safety of stereotactic radiosurgery through the performance of an hypophysectomy and/or chiasmopexy.



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Keywords: Cavernous sinus, meningioma, skull base, surgery, endoscopy, radiosurgery, radiotherapy

INTRODUCTION

Meningiomas account for one third of primary intracranial tumors with an incidence of 3-8 per 100,000 persons^[1]. They represent more than 40% of lesions involving the cavernous sinus (CS)^[2]. CS meningiomas originate or invade the parasellar space: they may start primarily within the CS or it may be involved secondarily in clinoidal or other sphenoid wing meningiomas, in addition to those arising from the tuberculum sellae or speno-petro-clival region. CS meningiomas are deeply located near critical neurovascular structures such as the optic pathways, the hypothalamo-hypophyseal axis, the internal carotid artery and its branches, and the oculomotor and trigeminal nerves. They may further extend into the supra and latero-sellar spaces, orbital apex and optic canal, sphenoid ridge, middle temporal fossa, and petroclival angle. The CS region, due to its complex anatomy and its particular position in the antero-lateral skull base, has always been a challenging area of treatment for neurosurgeons.

As with the great majority of intracranial meningiomas, CS meningiomas are WHO grade I tumors with a very slow growing rate. Their surgical treatment may result in significant neurological morbidity and even death. For this reason, the management of these patients should be multidisciplinary discussed according to the size, extension, clinical presentation, and evolutive pattern to grant the patients the longest survival possible with the lowest cranial nerve morbidity.

Small and asymptomatic meningiomas are often managed conservatively^[3]. In general, 15% of patients have neurological deficits at presentation^[4,5]. Ophthalmoplegia, secondary to tumor growth or as a complication of treatment, can represent a serious issue that strongly impairs the quality of life of these patients, affecting their self-image and their private and professional life. Thus, a balance between the different therapeutic options should be found for symptomatic CS meningiomas. A complete preoperative endocrinological assessment and an ophthalmological evaluation should be performed for every patient with visual complaints and/or radiological compression of the optic apparatus.

Symptomatic meningiomas enclosed in the cavernous sinus are offered up front radiosurgery or stereotactic fractionated modality. Tumors presenting a lateral extension should be addressed through a transcranial approach for the resection of the extracavernous portion. In surgical series, recurrences and progression free-survival rates range from 6% to 25% and from 4.5% to 65%, respectively, while the mortality rate varies between 2% and 7% and the morbidity from 10% to 65%^[6-8]. Thus, the results in terms of complete tumor removal, preservation of neurological functions, and quality of life do not always correspond to the expectations. Saberi *et al.*^[9] showed that the most important variable influencing the surgical outcome was the grade of encasement of nerves and vessels. The histological type, extent of dural attachment, and relationship and encasement with neurovascular structures should thus be carefully considered for the optimal management of CS meningiomas.

With CS meningiomas presenting a medial extension into the sphenoid sinus or extending into the antero-inferior portion of the CS, an endonasal approach can be performed as the tumor itself may create a safe space between the anterior dura and the internal carotid artery (ICA). Over the last few decades, endoscopic endonasal approaches have remarkably developed with the development of extended approaches^[10-14]. Through the transnasal route, it is possible to safely remove the tumor with a partial debulking, to decompress the optic canal or to perform a tissue biopsy when the diagnosis is not clear, particularly when another histological nature is suspected (lymphoma, granuloma, ectopic pituitary adenoma, neurofibroma, cavernous hemangioma, *etc.*)^[15-19]. The goals of endoscopic endonasal procedures

Table 1. The advantages and disadvantages of the different surgical approaches for cavernous sinus meningiomas are here summarized

	Transcranial surgery	Endoscopic surgery	Radiosurgery
PROS	To address the extracavernous portion of the tumor in the temporal fossa To address the supraclinoid portion of the tumor lateral to the ICA or with an encasement To decompress the lateral portion of the optic canal	Direct access for optic nerve and pituitary gland decompression To avoid brain retraction and manipulation To interpose autograft fat to protect radiosensitive structures (optic nerve and pituitary gland)	Non-invasive procedure Low risk of complications Good control rate (equivalent to Simpson grade I)
CONS	High risk of cranial nerve palsy if the lateral wall of the CS is entered Risk of vascular injury Risk of damage of brain parenchyma/epilepsy	Limited resection of the lateral portion of the tumor Risk of vascular injury and of cranial nerve palsy Risk of hypopituitarism Risk of CSF leakage	Tumor too close to pituitary gland and optic nerve are a relative contraindication No pathological analysis Limited to small volumes No decompression, thus less chance to improve pre-existing symptoms

CS: cavernous sinus; CSF: cerebrospinal fluid; ICA: internal carotid artery

are: (1) to perform an adequate bony decompression of the cavernous sinus, sella turcica and optic canal in cases with optic nerve compression; (2) to obtain tissue for a pathological analysis and a genomic profiling; (3) to reduce the volume of tumor to be treated by radiosurgery; and (4) to perform an hypophysectomy or chiasmectomy and allow a safer irradiation at a later date.

In most cases, the combination of a less aggressive surgical approach with a complementary radiation treatment seems to be the best management^[20,21]. Indeed, aggressive surgical resections are associated with a higher risk of complications and do not improve the natural history of the disease or the global outcome except in carefully selected cases^[22,23] [Table 1]. Furthermore, many of these tumors tend to recur over the long term. The combined treatment should be realized in tertiary care centers with a large experience in this area and a sufficient caseload [Figure 1].

Herein, we detail the relevant endoscopic endonasal anatomy of the cavernous sinus region and review the results of the surgical series reported in the literature dealing with the endoscopic endonasal management of CS meningiomas.

ENDOSCOPIC ANATOMY

The cavernous sinus is a paired venous sinus surrounded by dural layers and located in the middle cranial fossa. It is limited medially by the sphenoid bone and the sellar region, and laterally by the mesial face of the temporal lobe. The posterior margin is limited by the posterior cranial fossa, while anteriorly the cavernous sinus reaches the superior orbital fissure and the inferior surface of the anterior clinoid process. Cavernous sinus floor extends from the anterior to the posterior clinoid process and faces the basal cisterns. The lateral dural wall of the cavernous sinus is composed of the outer dural layer and the inner membranous layer. The inner layer contains the most critical nervous structures. The existence of a medial dural wall separating the pituitary from the CS remains a matter of debate^[24]. The CS contains multiple neurovascular structures: the sympathetic plexus around the internal carotid artery, the oculomotor nerves (III, IV, and VI) and the first and second roots of the trigeminal nerve (V1 and V2). In a cranio-caudal direction the III, IV, V1, and V2 course within the lateral wall of the sinus, while the VI cranial nerve is positioned within the CS, just lateral to the ICA [Figures 2 and 3].

To reach the CS through an endoscopic endonasal corridor, the extent of the approach varies from a standard transsphenoidal approach to more extended accesses, which include transpterygoid approaches

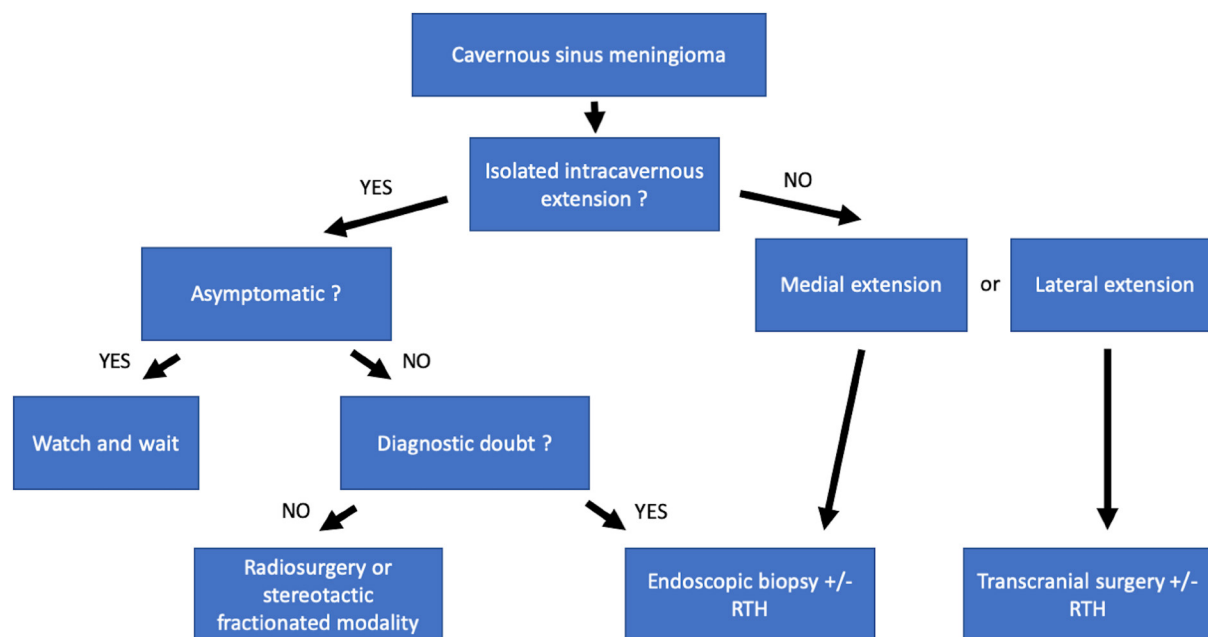


Figure 1. Algorithm showing the management of patients with cavernous sinus meningiomas according to the extension of the tumor and the clinical presentation or the doubt on the histological diagnosis. RTH: radiation therapy

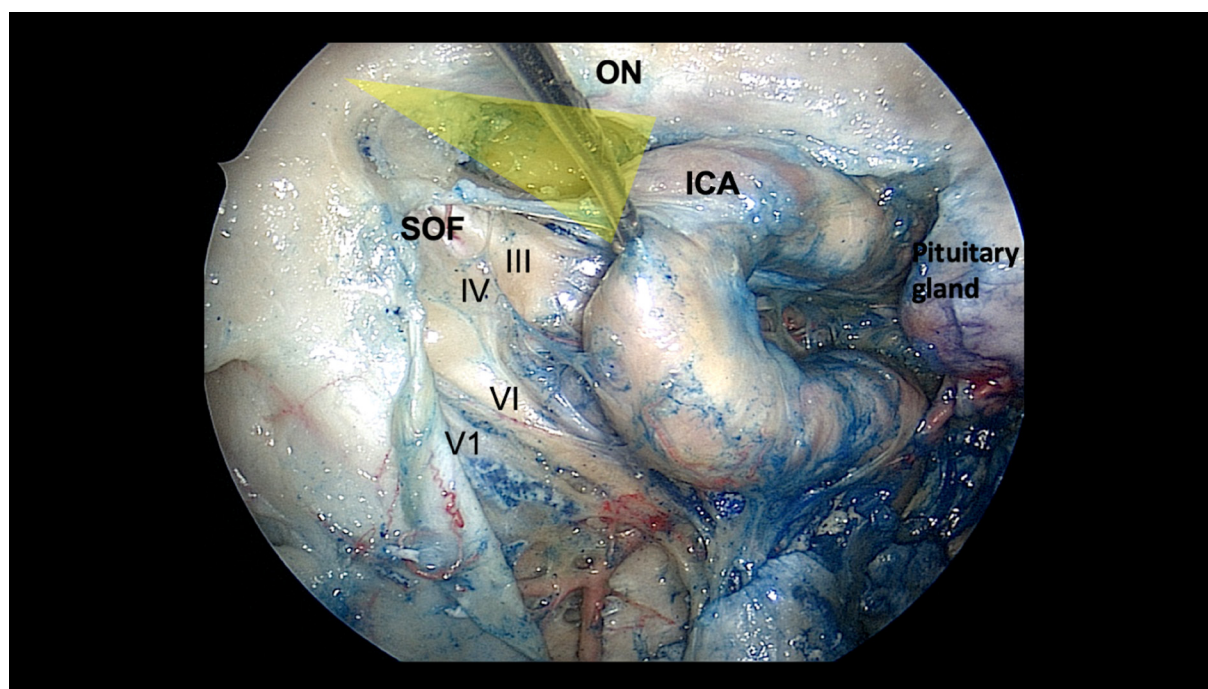


Figure 2. Endoscopic endonasal view of the right CS in a cadaveric specimen. The bone covering the CS was completely drilled to expose the ICA, the oculomotor nerves (III, IV, and VI) going to the SOF, and the first branch of the trigeminal nerve (V1). Superiorly, the ON is still covered by a thin layer of bone. The lateral optico-carotid recess is colored in yellow. Medially, the pituitary gland is also exposed. CS: cavernous sinus; ICA: internal carotid artery; ON: optic nerve; SOF: superior orbital fissure

with anterior and posterior ethmoidectomies and vidian canal dissection. The anatomy of the sphenoid sinus in terms of pneumatization and presence of septa should be carefully considered on preoperative imaging. The sphenopalatine artery courses at the inferior portion of the sphenoid ostium and should

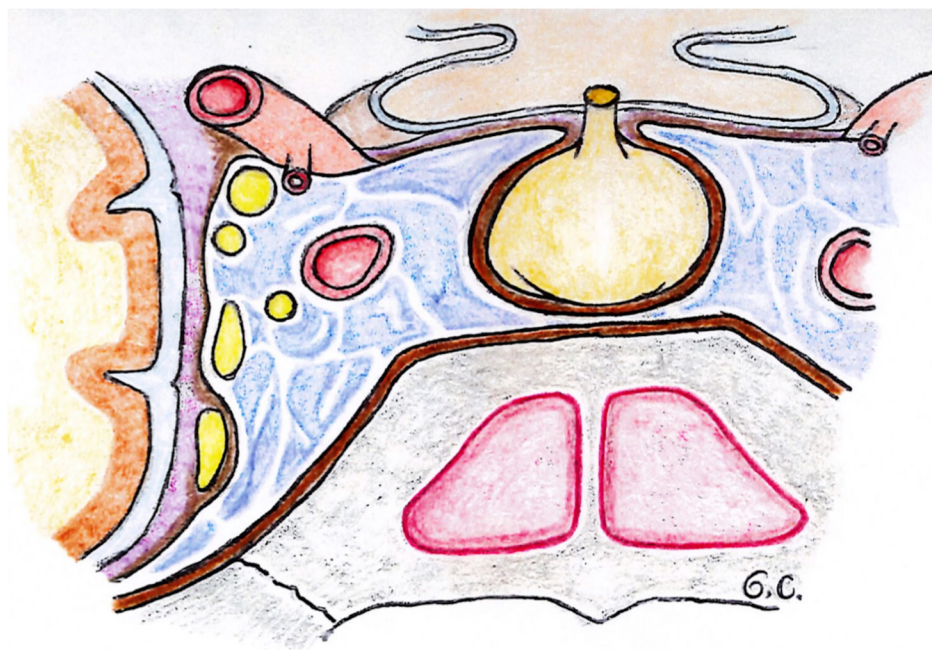


Figure 3. Schematic representation of the right cavernous sinus. The III, IV, V1, and V2 course within the lateral wall of the sinus in a craniocaudal order, while the VI cranial nerve is the only one inside the cavernous sinus, just lateral to the internal carotid artery

be preserved. Once the sphenoid sinus is entered, the sellar floor is identified in the midline with the tuberculum sellae and the landforms of the optic canals superiorly and laterally, as well as the carotid prominences laterally. The medial and lateral optico-carotid recesses are also recognized [Figure 4]^[25]. Within the sphenoid sinus, the anterior CS corresponds to the anterior carotid prominence, easily identified on the lateral sphenoid sinus wall.

In cases where a transpterygoid approach is performed, the bony anatomy of the maxillary and ethmoid sinuses should be analyzed. The pterygopalatine fossa is a pyramidal space located between the pterygoid bone posteriorly, the palatine bone anteromedially, and the maxillary bone anterolaterally^[10,11]. Once the maxillary sinus is entered, the infraorbital nerve is a consistent landmark and the pterygopalatine fossa is medial to it. It has a rich vasculonervous content, namely the third segment of the maxillary artery and its branches (anterior compartment of the fossa) [Figure 5], the pterygopalatine ganglion, the greater and lesser palatine nerves, the maxillary and infraorbital nerves, and the vidian nerve (posterior compartment)^[10-14]. The anterior opening of the vidian canal is located medially while the foramen rotundum is located laterally^[10]. Foramen lacerum and petrous ICA may be exposed following the vidian nerve postero-medially, while the lateral portion of the clival recess is the landmark for the medial wall of the paraclival ICA. The foramen rotundum can also be used as an anatomical landmark for the antero-inferior wall of the CS during extended approaches.

IMAGING

Both CT-Scan and MRI are essential to assess the bony and neurovascular relationships of the meningioma. MRI shows the exact location and the extension of the meningioma. It helps in defining the limits of the tumor in relationship with the neurovascular structures inside and outside the CS. T2-weighted coronal sequences allow a good analysis of the meningioma's relationships with the CS dural layers [Figure 6]. The distance from the optic pathways, the cranial nerves anatomy, and the pituitary region can also be carefully appraised particularly using CISS-3D or FIESTA sequences as well as cranial nerve tractography.

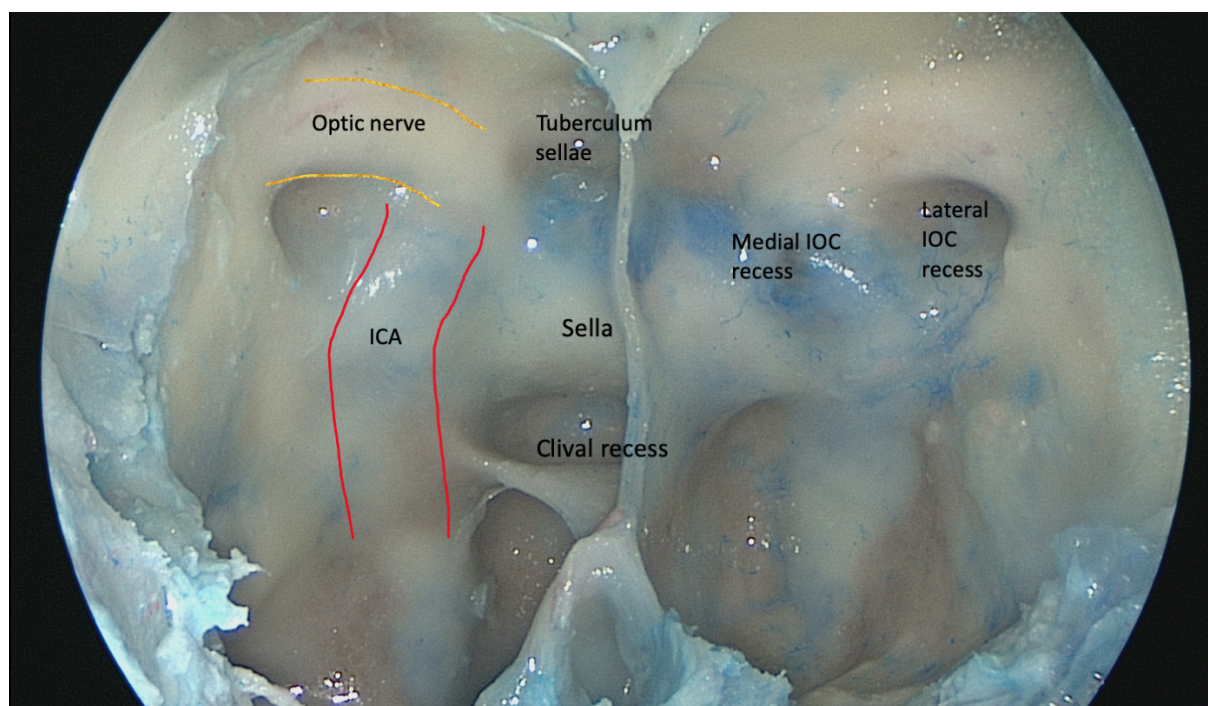


Figure 4. Endoscopic endonasal view of the posterior wall of the sphenoid sinus in a cadaveric specimen. A midline septum was partially drilled. In the midline, in a craniocaudal direction, the tuberculum sellae, the sella, and the clival recess are evident. Laterally, the carotid prominence (red lines) and, superiorly, the optic nerve (golden lines) are delimited. The medial and lateral IOC recesses are also marked. ICA: internal carotid artery; IOC: interoptico-carotid



Figure 5. Coronal view of the pterygo-palatine fossa in a cadaveric specimen. Once that the posterior wall of the maxillary sinus is opened, the maxillary artery and the pterygopalatine ganglion are exposed (left). A large sphenoidotomy is performed to illustrate the close relationships between the different structures. Once that the vidian nerve is identified, it can be followed posteriorly until the foramen lacerum and the petrous ICA (right). ICA: internal carotid artery

High-resolution contrast-enhanced axial MRI is necessary in the preoperative planning and fat suppression images may be used for tumors adjacent to the orbit or when a chiasmectomy has been previously performed. The angio-MRI is useful to delineate the caliber and the displacement of the ICA and its branches, while the MR-venography illustrates the venous drainage of the skull base^[26]. A detailed study of the ICA course and of the collateral systems is fundamental before starting the resection of a CS meningioma.

Thin-slices bone CT scan is valuable to study the presence and direction of septa and the degree of pneumatization of the sphenoid sinus, the anatomy of the anterior and posterior clinoid processes, the sella turcica and the orbital apex, the sphenoid wing and its foramina, and the petrous apex. The invasion of

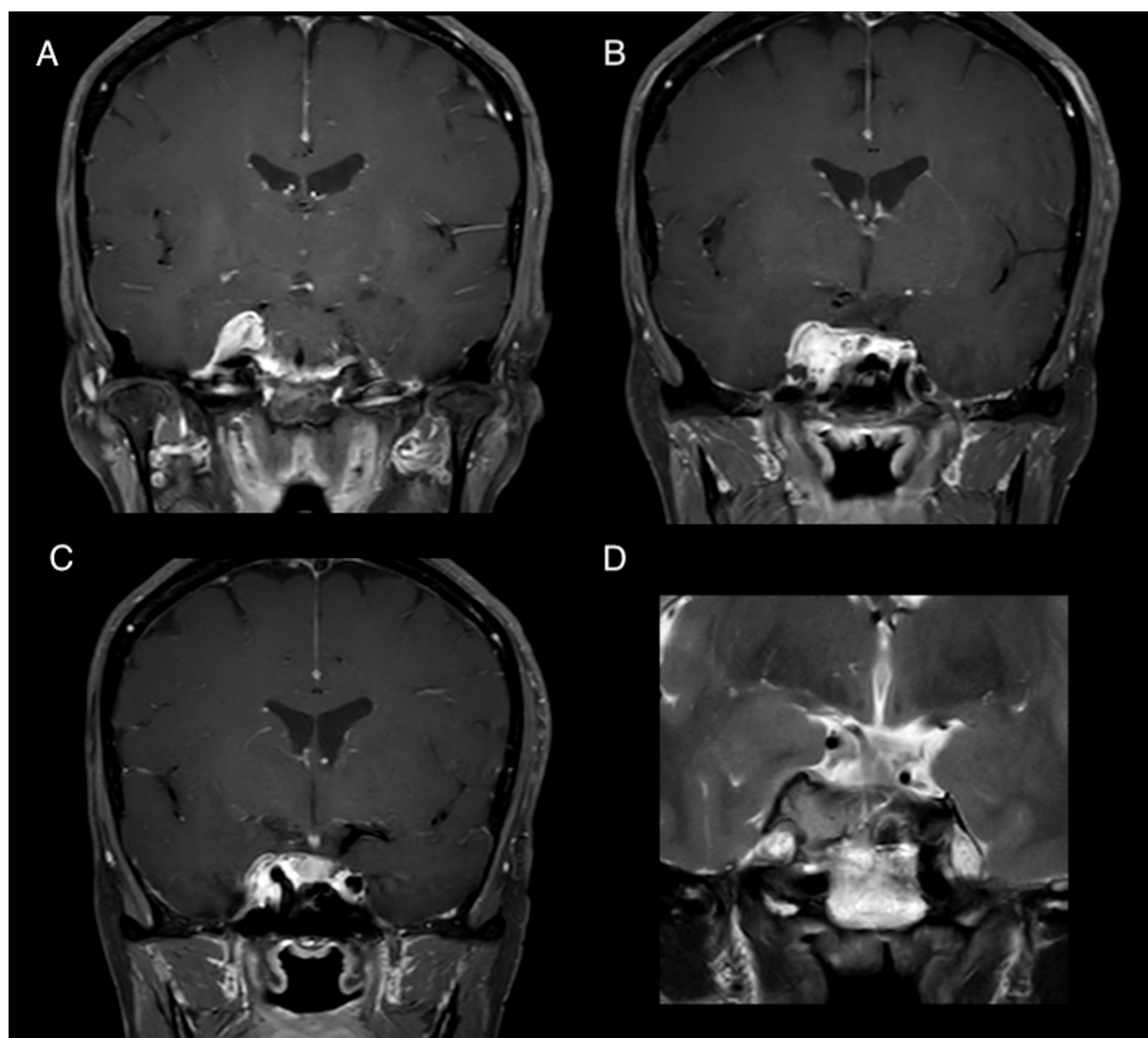


Figure 6. Coronal view of a cerebral MRI showing a meningioma in the right CS. The asymmetry between the row cavernous sinuses is evident and the lesion present a strong contrast enhancement after gadolinium administration (A-C). The relationships between the meningioma and the lateral wall of the CS and the optic apparatus are better defined through the analysis of T2-weighted sequences (D). CS: cavernous sinus

the optic canal and the superior orbital fissure, as well as rotundum, ovale, and lacerum foramina, should be checked for, as well as the potential invasion of the sphenoid sinus. The presence of osteolysis or bone reactive hypertrophy should be carefully evaluated. The latter in particular could reflect tumoral infiltration and may be the target for extensive drilling.

While angio-MRI and angio-CT have progressively lessened the need for digital subtraction angiography, this may be useful to evaluate the collateral network, particularly in case of ICA narrowing using balloon occlusion tests.

SURGICAL TECHNIQUE

The endonasal approach to address CS meningiomas has the advantage of avoiding brain retraction and manipulation, with a straightforward access to decompress the optic nerve, pituitary gland, and cranial nerves. The endoscope allows a panoramic visualization and a more lateral exposure when compared to

microscopic endonasal approaches^[27]. This permits the performance of a precise bony decompression around the sella, the medial cavernous sinus, the optic canal, and, if necessary, of the clivus and Meckel's cave^[17]. Furthermore, this approach allows the positioning of autograft fat between the tumor and radiosensitive structures for further treatments^[28].

After induction of general anesthesia, the endotracheal tube is positioned on the left of the patient and the head should be slightly tilted to the left, turned to the right, and slightly flexed as for a standard endoscopic endonasal transsphenoidal approach. The neuronavigation system is positioned to guide the procedure and the volumetric MRI is fused with the bone-window CT to increase the precision of target definition. Intraoperative monitoring is useful to monitor the function of the oculomotor and trigeminal nerves. The face, the right periumbilical area, and/or the thigh are draped for graft harvesting if necessary.

In general, a binostril bimanual technique is preferred to obtain a wider range of movement. The primary surgeon operates with dissecting instruments and the drill from the right nostril, while the assistant surgeon manages the endoscope in the right nostril and the suction in the left nostril to keep the surgical field clear. Alternatively, a contralateral uninostril approach can also be an option. The right middle turbinate can be resected to widen access if needed during the procedure. Once the sphenoid ostium is identified medial to the superior turbinate and superior to the choana, a wide sphenoidotomy is performed with a posterior septostomy. A large exposition of the sphenoid sinus is necessary to identify the posterior wall landmarks, including the tuberculum, sellar floor, and clival recess in the midline, as well as the optic canals, carotid prominences, and optico-carotid recesses laterally.

A key part of the procedure is bony decompression of the sella, cavernous sinus, optic canal superiorly, and upper clivus when necessary. The bone is generally removed with a high-speed diamond burr and the ultimate eggshell layer is removed with a Kerrison rongeur to safely expose the dura. Constant irrigation should be performed during the drilling to avoid thermic lesions to delicate neuro-vascular structures. The medial and the anterior wall of the cavernous sinus are exposed after the ipsilateral side of the sella is exposed. The medial optico-carotid recess is then progressively exposed. The optic canal unroofing is one of the most important steps, which should be carefully performed as this could induce visual deterioration^[29]. This part of the procedure is necessary when there is a reduction in the caliber of the optic canal and/or when the patient presents with an optic neuropathy. Doppler ultrasound and neuronavigation are useful to localize the ICA during the osseous decompression and before dural opening. Tumor removal should be performed selectively with the goal of decompressing the optic nerve, the pituitary gland, and the cranial nerves into the cavernous sinus. The medial portion of the tumor invading the sella should be initially removed [Figure 7].

Subsequently, the dura over the cavernous sinus can be opened in a lateral to medial direction to avoid injury of the ICA. Brisk venous bleeding is common after tumor removal and can be controlled with hemostatic agents and temporary mechanical packing. A nerve stimulator is used to localize the course of VI cranial nerve once the CS is entered. Visualization of cranial nerves is not necessary and often dangerous. Electrocautery in the area should be avoided to prevent thermal injuries. Excision of the tumor is done in a piecemeal fashion with curettes and ultrasonic aspiration (particularly useful with fibrous tumors). The integrity of the lateral wall and the roof of the cavernous sinus should be respected. At the end of the resection, a hypophysopey is performed with the positioning of small pieces of fat between the residual tumor and the pituitary gland to fill the dead space created by tumor removal and to better delineate the target and provide a margin for adjuvant radiosurgery in order to protect radiosensitive structures. In general, when a biopsy is performed for purely intracavernous lesions, there is no CSF leakage. An artificial dural substitute or fascia lata from the thigh and glue are sufficient for skull base reconstruction. A nasoseptal flap is rarely required. An endocrinological assessment should be performed in the postoperative period and records are kept for fluid intake and urine output.

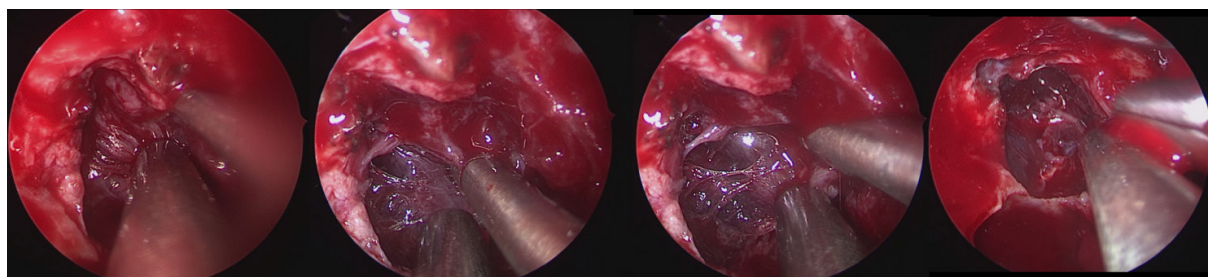


Figure 7. Intraoperative pictures showing the endoscopic resection of an infradiaphragmatic meningioma invading the right cavernous sinus. The resection should start from the intrasellar portion and then proceed towards the cavernous sinus. A complete removal of the meningioma invading the medial portion of the cavernous sinus was possible in this case

REVIEW OF REPORTED SURGICAL SERIES

We performed a literature review on PubMed database up to April 2020 to summarize the surgical series treating patients with CS meningiomas through endoscopic surgery followed or not by adjuvant radiotherapy. The articles were identified using Boolean searches with the keywords “endoscopy” AND “cavernous sinus” AND “meningioma”. Table 2 shows in detail the surgical results and the final outcome. Nine series published between 2009 and 2020 gathered 106 patients in whom an endoscopic endonasal approach was performed for CS meningiomas^[18,28,30-36]. In most of cases, the aim was to perform a tissue biopsy and decompression of cranial nerves in the CS or optic nerve. gross total resection was performed only in rare cases^[18,33-35].

In only nine cases (8.5%), a worsening of the cranial nerve palsy was recorded, while in three out of 97 cases (3%) a new endocrinological deficit occurred. The surgical complications reported were: CSF leakage in three cases, one case needed a ventriculoperitoneal shunt but he was operated through a combined approach (endoscopic and transcranial), and two patients experienced an ICA injury (one died from a hemispheric infarct). Forty-three out of 64 patients (67%) reported an improvement in CN palsy in the postoperative period and 22/41 (53.6%) had an improvement in their pituitary function. Adjuvant radiation therapy was administered in 43/78 patients (55%). The protocols of radiation therapy administered varied from stereotactic radiotherapy (RT) to radiosurgery or particle beam irradiation and when specified the tumor control was excellent at a mean follow-up of 39 months. Only one complication of stereotactic RT was reported with the development of a pituitary insufficiency after the treatment.

Endoscopy might enhance the efficacy and safety of stereotactic radiotherapy or radiosurgery. This might be due to the fact that during surgery an adequate distance can be created between the tumor and the pituitary through the resection of the meningioma, thus allowing a safer irradiation. Furthermore, the interposition of abdominal fat (hypophysopepy) between the meningioma and the pituitary gland may limit the risk of post-radiation endocrinopathies.

In summary, from these studies, we can conclude that a biopsy or planned partial tumor removal may be safely performed, coupled with bony decompression, to improve the visual symptoms and obtain a decompression of the cavernous sinus. Better results in terms of symptomatic improvement were obtained in the cohort of previously untreated patients^[28].

Furthermore, endoscopy may improve or stabilize pre-existent cranial neuropathy and endocrinopathy (67% of patients in Lobo's series improved their endocrinopathy and 42% of patient improved or resolved their cranial neuropathy)^[32].

Table 2. Summary of the surgical series reporting an endoscopic management of patients with cavernous sinus meningiomas

	No. pts	Treatment plan	Postop new CN palsies	Postop new endocrinopathies	Other complications	CN palsy improvement	Endocrinological improvement	RT protocol	Mean FU	Tumor control
Akutsu <i>et al.</i> [30] 2009	21	17 Surgery + RT 4 only surgery	0	1	0	15/17 (88.2%) Or 32/34 (94%)	16/28 (57%)	13 SRT 2 SRS 2 PBRT	71 mo	100%
Liu <i>et al.</i> [36] 2009	2	Surgery +/- RT	0	0	1 CSF leakage	NS	NS	1 RT	NS	NS
Grailon <i>et al.</i> [31] 2014	2	STR + SRS	0	0	0	2	NS	SRS	18 mo	2 (100%)
Khan <i>et al.</i> [33] 2014	9	8 STR 1 GTR	1/7 (14%)	NS	1 VP shunt and 1 meningitis (also transcranial approach performed)	5/7 (71%)	NS	6 RT	14 mo	NS
Zhang <i>et al.</i> [18] 2014	6	4 GTR 2 STR	0	0	0	NS	NS	None	37 mo	NS
Lobo [32] 2015	15	9 surgery 6 surgery + RT	1	0 (1 after SRT)	NS	8/15 6 stable	4/6 (67%)	6 SRT	21 mo	10 controlled (6/6 or 100% pts with surgery + SRT) 5 progression NS
Koutourousiou [35] 2017	28	2 GTR 14 STR	4 (14.3%)	2 (7.1%)	1 CSF leak 1 DVT (3.8%) 2 ICA injuries (7.1%; 1 died)	NS	NS	NS	NS	NS
Sivakumar [28] 2019	20 (6 previous TT)	Surgery + SRT if no previous RT and growth at FU	1 immediate 2 delayed TOT 3/8 (38%)	0	1 CSF leak and meningitis	8/14 (57%) 2/6 (33%) 4/6 pts with ON decompression had improvement (66%)	2/7	SRT 54Gy in 30fr 11/14	57 mo	14/14 pts with no previous RT (100%) 2/6 with previous TT controlled tumor 2/6 died 3 (100%)
Zhang [34] 2019	3	Only surgery 1 GTR 2 STR	0	0	0	3	NS	None	54 mo	3 (100%)

CN: cranial nerve; CSF: cerebrospinal fluid; DVT: deep venous thrombosis; GTR: gross total resection; PBRT: proton beam radiotherapy; fr: fractions; FU: follow-up; Gy: gray; NS: not specified; ON: optic nerve; RT: radiotherapy; SRS: stereotactic radiosurgery; SRT: stereotactic resection; STR: subtotal resection; TOT: total; TT: treatments; VP: ventriculoperitoneal

COMBINED AND ADJUVANT STRATEGIES

From a radiobiological point of view, meningiomas are considered as late responding tumors and they can be better controlled with a higher dose/fraction rather than conventional fractionation, as explained in the meta-analysis performed by Leroy *et al.* [37], where radiosurgery (RS) achieved a twice-higher rate of tumor volume regression than fractionated radiotherapy. This explains why the use of Gamma Knife or dedicated Linac/Cyberknife systems may offer the possibility to obtain excellent outcomes in terms of local control with reduction of treatment associated risks [37]. Precise delineation of target volumes (TV) with selective coverage and steep radiation falloff with sparing of normal tissues are the keys to a successful treatment.

RS can be considered as first line treatment for small symptomatic CS meningiomas if they present a safe distance from the optic pathway^[38-43]. For large meningiomas, a single fraction RS may be problematic as the risk of damaging healthy tissues is high and a complication rate of 21% *vs.* 3% was reported for meningiomas larger than 10 cm³ *vs.* smaller lesions respectively^[44]. Furthermore, the distance between the optic apparatus and the tumor should be carefully considered before choosing the primary treatment: a distance of at least 5 mm between the meningioma and the optic nerve is considered safe^[45,46]. Thus, when the meningioma is large or too close to the optic pathways, a combined approach with a surgical partial decompression followed by adjuvant radiation therapy should be preferred.

Whether RS should be routinely performed in the months after surgery or only in cases of postoperative tumor progression is still a matter of debate. Considering the natural history of meningiomas, we know that they have a slow tendency to grow but about one fourth of all the meningiomas, in particular those calcified, do not seem to grow^[47]. In common practice, the irradiation is generally performed 3-6 months after surgery, while, for minimal residual tumors, radiation is performed when a growth is visible on follow-up images. This waiting time should help in the recovery of cranial nerves and pituitary gland surgical manipulation^[32]. For atypical meningiomas or meningiomas showing an aggressive behavior with a higher growth rate, radiotherapy should be performed in a shorter period of time^[32]. Beside the histological grade, the previous treatments performed should also be taken into account before planning the treatment. The inclusion of the dural tail in the TV is matter of debate, and, when an irregular shape is present, the dose distribution should be accurately checked^[48-50].

For radiosurgical treatments, the dose recommended is between 12 and 15 Gy, which allows a good compromise between tumor growth control and local neurotoxicity. The risk of damaging the optic apparatus exists when the dose (to nerve) received is more than 8 Gy. The oculomotor nerve in the cavernous sinus tolerates doses greater than 20 Gy while the trigeminal nerve is at risk with doses beyond 19 Gy. However, in common practice, the lateral wall of the cavernous sinus, the pituitary gland, and stalk, the hypothalamus and brainstem should not receive more than 15 Gy.

In their review of the outcomes of large radiosurgical series, Fariselli *et al.*^[51] showed progression free survival at 5 and 10 years of 80%-100% and 73%-98%, respectively, and a radiological volume reduction was observed in 29-69% of cases. No mortality was described as secondary to radiation therapy, while the reported morbidity included new neurologic symptoms or symptoms of neurotoxicity (optic neuropathy, pituitary dysfunction, diplopia, and radiation-induced edema), which ranged from 6% to 27.5%^[52-55]. A meta-analysis comparing primary RS *vs.* surgery followed by adjuvant RS showed a lesser rate of neurological morbidity in the primary RS group (27.5% *vs.* 59.6%)^[55]. Kano *et al.*^[56] reported that improvement in cranial nerve palsies was less likely to occur in patients who had undergone previous surgery when compared to those treated with radiosurgery alone (14% *vs.* 39%). One explanation may be that operated patients had permanently damaged cranial nerves as a result of the surgery. It is well described that about 75% of recurrences occur outside the treatment field and this reflects the paramount importance that needs to be placed on the contouring phase of the treatment^[57].

For recurrent meningiomas, data on the efficacy of repeated RS are limited. Mifepristone and bevacizumab have been described as promising agents for recurrent tumors, but these results still need to be validated in larger studies. Nonetheless, these drugs, which target tumor receptors, highlight the importance of obtaining a histological diagnosis and genomic profiling before their introduction to select effective targeted therapies^[58,59].

CONCLUSION

The management of CS meningiomas depends on the size and extension of the tumor and on the clinical manifestations of the patient. The treatment decision varies among a simple annual clinico-radiological

follow-up, transcranial or endoscopic surgery according to the extension of the tumor, radiation therapy, or the combination of both. The main goal of the treatment is to prevent growth and to avoid or prevent neurological deficits. For symptomatic meningiomas extending into the antero-inferior portion of the cavernous sinus, a direct endoscopic transcavernous approach should be preferred. It represents a safe procedure, with a very low complication rate when patients are carefully selected in a tertiary level center, with good improvement rates or at least stabilization of cranial neuropathies and endocrinopathy. Multidisciplinary recommendations for a specific treatment carries an important ethical responsibility and it is the duty of each surgeon to propose the best management to each patient keeping in mind the risk-benefit analysis.

TRICKS

1. An endoscopic transcavernous biopsy/partial removal is easily performed when the meningioma is located in the antero-inferior portion of the CS.
2. Intraoperative neuronavigation and careful understanding of preoperative anatomy are key factors in safely performing the procedure.
3. Fully endoscopic procedures should be preferred to microscopic procedures performed under endoscopic assistance for the better panoramic view allowed by the endoscope.
4. Doppler ultrasound is invaluable in localizing the carotid artery inside the tumor and guide tumor removal.
5. Bony decompression of the optic canal is a key step of the procedure to increase the chance of visual improvement.
6. Autologous fat can be interposed between the residual tumor and the pituitary gland to limit the risks of hypopituitarism after adjuvant radiation therapy.
7. A careful reconstruction should be performed to avoid postoperative CSF leakage.
8. Meningiomas better respond to higher dose/fraction of radiation therapy, and a gamma knife/Cyberknife/Linac treatment should be preferred.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis: Cossu G, Berhouma M, Messerer M

Performed data acquisition, as well as provided administrative, technical, and material support: Abarca J, Levivier M, Starnoni D, Daniel RT

Availability of data and materials

Not applicable.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Not applicable.

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Review

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Robotic or laparoscopic surgery for rectal cancer - which is the best answer? a comprehensive review of non-oncological outcomes and learning curve

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Abstract

Much effort has been spent evaluating the difference between robotic and laparoscopic surgery platforms for rectal cancer. There is a plethora of literature comparing outcomes for intraoperative events, postoperative complications, long term outcomes, cost, and learning curve. The data are conclusive regarding the higher cost of robotic surgery compared to laparoscopic surgery. This article is a comprehensive review of the available literature regarding intraoperative and postoperative outcomes. For practically all parameters evaluated, there are no significant differences between the two platforms. The ultimate decision on whether to perform robotic vs. laparoscopic surgery should be based on surgeon preference and familiarity with equipment, as well as local resources.

Keywords: Rectal cancer, rectal carcinoma, robotic, robotics, laparoscopy, total mesorectal excision

INTRODUCTION

Surgical management of rectal cancer has undergone an impressive evolution during the past thirty years. An explosion of minimally invasive techniques has advanced almost every colorectal operation since the first reports of laparoscopic segmental and total colectomy^[1]. Advantages of laparoscopic surgery compared to laparotomy include reductions in postoperative pain, length of stay, incisional hernia, adhesive



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bowel obstruction, wound complications, and mortality^[2-5]. The disadvantages of laparoscopic surgery comprise a relative loss of tactile sensation compared to open surgery and technical difficulty with fine movement. There is heightened awareness of surgeon ergonomics due to overuse injuries and workplace musculoskeletal disorders in laparoscopic surgeons. Improper table height, position of the monitors, and handling of long instruments are factors contributing to these afflictions.

The introduction of the robotic DaVinci operating system (Sunnyvale, CA) in 2000 brought forth another dimension of minimally invasive technology. This platform was utilized in colorectal surgery in March 2001 when the first sigmoid and right colectomies were described^[6]. Robotic surgery has now gained widespread acceptance both in terms of surgeon satisfaction and patient outcomes. The strengths of robotic surgery lie principally in wristed instruments providing seven degrees of freedom. Many surgeons endorse greater comfort during the procedure, improved visualization of the operative field, and less technical difficulty operating in challenging locations including the narrow pelvis. The limitations of robotic surgery can include the operative time required to dock the robot, loss of tactile sensation, and increased cost compared to laparoscopic surgery.

Standards by which successful surgical outcomes are evaluated examine intraoperative events, postoperative complications, and long-term sequelae. These facets have been extensively studied comparing laparoscopic and robotic surgery. This paper explores any potential differences between the two methods regarding non-oncological perioperative outcomes. Conversion rate, postoperative pain or ileus, anastomotic leak, surgical site infection, length of stay, cost, long-term urogenital function, and learning curve are the specific topics that are addressed.

INTRAOPERATIVE OUTCOME

Conversion rate

Challenges that present to a surgeon include patient body habitus, fibrosis from chronic inflammatory processes, adherence to surrounding structures by infiltrating tumours, and adhesions from previous surgeries. These situations can result in conversion to an open procedure. One of the unique tasks specific to colorectal surgeons is removing a low rectal tumour. Particularly in a narrow pelvis, this task can be challenging due to the limited range of motion of laparoscopic instruments. Colorectal robotic surgery first gained popularity specifically for this scenario. Precise dissection down to the pelvic floor with wristed instruments facilitates total mesorectal excision over the pelvic brim.

Given the above situations, investigators hypothesized that robotic surgery would result in a lower conversion rate compared to laparoscopic procedures, but the data exhibit many conflicting reports when examining conversion rates. One must consider the research design when interpreting these results. A few studies utilized nation-wide databases, while others performed retrospective reviews, case-matched studies, or propensity-matched groups. Several studies report equivalent conversion rates between laparoscopic and robotic procedures^[7-10]. Feinberg *et al.*^[11] performed a retrospective National Surgical Quality Improvement Program study of over 8,864 patients undergoing either laparoscopic or robotic colorectal procedures, finding a statistically significant difference in the conversion rate of 13.7% and 9.5% for laparoscopic and robotic procedures, respectively ($P < 0.008$). A subgroup analysis was performed to identify risk factors for increased conversion rates, finding that patients with colon cancer [odds ratio (OR) 1.8], Crohn's disease (OR 2.19), and diverticular disease (OR 1.9) had higher likelihood of conversion. The two most interesting findings in this study were that neither body mass index $> 30 \text{ kg/m}^2$ nor rectal resection procedures conferred a significant risk of conversion to open. These findings are noteworthy because body habitus and pelvic operations had been theorized as situations in which the use of the surgical robot would confer an advantage.

Another comprehensive study of 2,735 patients showed a significantly higher rate of conversion in the laparoscopic compared to robotic group. This was found throughout the general cohort as well as in rectal specific procedures, which had a conversion rate of 7.8% *vs.* 21.2%, respectively ($P < 0.001$)^[12]. While these studies boast large sample sizes, the two arms were unevenly matched in terms of number of patients, which may have affected the results. This issue is common throughout the literature on this topic, given the novelty of robotic surgery. A meta-analysis of four randomized controlled trials (the highest quality evidence available), found a significant difference in conversion rates of patients undergoing colorectal resections for cancer. The robotic procedures had lower rates of conversion to open (1.82%) *vs.* laparoscopic procedures (9.48%), $P < 0.04$ ^[13].

Upon review of this data, one can safely argue that robotic procedures are associated with lower rates of conversion compared to laparoscopic surgeries. However, it should be noted that there are many confounding factors which may affect these results. Patients with a hostile abdomen, advanced tumours, or other considerations may be planned to undergo laparoscopic instead of robotic surgery if the surgeon is anticipating a high likelihood of conversion. Other scenarios may have presented with unexpected intraoperative findings that would have required the case to be converted no matter which modality was used.

Operative time

Successful performance of surgery is not measured by the time required to perform the task. However, increased operative time correlates with many adverse perioperative outcomes. Data collected across all surgery specialties demonstrates that operative time was 30 min longer in patients with surgical site infections than in those without^[14]. Increased operative time has also been shown to result in higher rates of ileus and length of stay^[15,16].

Advocates for laparoscopic surgery often attribute the time needed to dock the robot as a drawback to robotic surgery. The progress of the surgery comes to a halt during this time, particularly with procedures spanning two abdominal quadrants that require a second docking of the robot. Robot docking times have a reported mean of 3-11 min^[17,18]. Longer operative times in robotic compared to laparoscopic surgeries were reported in earlier studies performed between 2010-2014^[9,12], however, later studies have found no difference in times comparing laparoscopic with robotic colorectal resections^[11,19].

Global utilization of the robot has enabled an international meta-analysis of 22 studies comparing operative times, demonstrating a significant difference in favour of laparoscopic over robotic procedures^[20]. Surgeon experience, case volume, and consistency of the operative team are major factors affecting operative efficiency for both methods. A more detailed analysis of operative time will be discussed below with an overview of the learning curve.

Cost

Laparoscopic instruments are repeatedly reusable, apart from energy devices and staplers which are discarded after one operation. Robotic instruments are calibrated for a finite number of uses per instrument; typically, after ten operations the instrument must be replaced. However, the individual instruments contribute to only a small part compared to the cost of using the platform. It is difficult to capture cost differences regarding the procedure itself, as many studies utilize the total cost of hospitalization as their endpoint. Alharthi *et al.*^[21] looked at sigmoid colectomies and found a cost difference of \$45,057 *vs.* \$57,871 in favour of laparoscopic procedures. This margin has been repeatedly demonstrated on subsequent studies including a meta-analysis of randomized controlled trials, with a reported average higher cost of \$8,000-\$10,000 for robotic procedures^[22,23].

A few studies have been successful in evaluating the cost differences between robotic and laparoscopic surgery examining only the charges specific to the procedure. Ramji *et al.*^[24] found the intraoperative robotic costs to be twice as much compared to laparoscopic costs. Some evidence exists that increased experience over time leads to fewer charges with robotic procedures. Al-Mazrou *et al.*^[7] found that, despite a significantly higher cost with the robot over a span of three years, the cost difference reduced over time for the robotic group: \$2698 in 2012, \$2235 in 2013, and \$1402 in 2014. Given the lack of significant differences in many perioperative parameters between the two groups, the cost associated with the robotic procedure is the one consistent metric upon which improvements can be made.

POSTOPERATIVE OUTCOMES

Pain

Robotic and laparoscopic surgery share similar incisions via trocar and specimen extraction sites. A robotic right colectomy typically involves an intracorporeal anastomosis, allowing for extraction through a Pfannenstiel incision at the conclusion of the procedure. Investigating this theory of a less painful incision, Kelley *et al.*^[25] reported a 50% lower use of postoperative narcotics in the robotic group compared to laparoscopic right hemicolectomies. Within the literature specific to rectal procedures, there are no statistically significant differences in postoperative pain scores or analgesic use between the two interventions^[18,26].

Ileus

There were no observed differences in several independent studies of laparoscopic *vs.* robotic rectal resections in terms of postoperative ileus. Pooled data from eight studies with 854 patients failed to reach significance regarding the incidence of prolonged ileus between the two groups, nor was there a difference in time to resumption of regular diet^[27]. Feinberg *et al.*^[11] reported ileus rates of 9.5% for robotic *vs.* 10.4% for laparoscopic rectal resections, which was not statistically significant. While the rates of ileus were as high as 12%-17% in another study, comparisons between laparoscopic and robotic surgery continued to show no difference. Conversely, a meta-analysis of over 125,989 patients undergoing colectomies did show a statistically significant faster time to recovery of bowel function in the robotic group, though these groups were vastly uneven (121,055 laparoscopic patients *vs.* 4,934 robotic patients)^[28]. Given the plethora of case-matched, well-performed studies listed previously, there is no clear difference in ileus rates between the two methods.

Surgical infection and anastomotic leak

Surgical site infection and anastomotic leak rates were not shown to be different between the robotic and laparoscopic surgery groups for rectal cancer in the ROLARR randomized clinical trial^[29]. The results from this international, multi-institutional study support the findings of four other independent studies demonstrating no significant difference between the two arms^[9,11,30,31].

Length of stay

Multiple studies have shown no difference in the length of stay between robotic and laparoscopic proctectomy^[9,32]. While two studies claim statistically significant differences in data (0.6 days and 0.4 days, both favouring robotic surgery), this does not translate into clinical relevance^[12,33]. Additionally, it is also hard to determine if the cost of hospitalization is affected due to the time difference. Many confounding variables can account for differences this diminutive, including wait times while admitted in holding prior to the procedure, operative times, and availability of transportation home on the day of discharge. A comprehensive review of the National Inpatient Sample database by Alharthi *et al.*^[21] did show a meaningful difference of 4.8 days for robotic *vs.* 5.7 days for laparoscopic approach. This study is the only one to also look at hospital charges, and despite a shorter length of stay the robotic group still had significantly higher hospital charges.

Urogenital/sexual function

Pelvic dissection carries a risk of urogenital dysfunction secondary to nerve injury, particularly during total mesorectal excision. Injury to the hypogastric plexus in the presacral space and the pelvic splanchnic nerves (nervi erigentes) in the pelvic sidewall can cause significant morbidity. Postoperative urinary retention and erectile dysfunction may result from damage to these nerves. Proposed benefits of the robotic platform include more precise dissection afforded by the wristed instruments and better depth perception due to the binocular lens. These two advantages are postulated to help identify and preserve these nerve branches to reduce morbidity. There is consensus in the literature that postoperative urinary function scores in women fail to show a difference between robotic and laparoscopic surgery^[29,34,35]. The standardized International Prostatic Symptom Score is typically used to measure male urinary function scores. Two prospective studies, as well as a meta-analysis, failed to show a major difference in male urinary symptoms at multiple time points postoperatively when comparing the two surgical techniques^[29,34,36,37]. Other studies revealed only minor differences regarding an earlier return to baseline function, or shorter time to catheter removal^[30,35].

Sexual function returns faster in patients after undergoing robotic procedures *vs.* traditional laparoscopy. Reviewing quality of life and sexual outcomes in robotic surgery specific to rectal cancer, there was no difference in erectile function comparing high *vs.* low anterior resection *vs.* abdominoperineal resection. Luca *et al.*^[38] examined only robotic procedures and reported a decrease in erectile dysfunction compared to baseline at 3 and 6 months, but returning to baseline in one year. The literature comparing sexual function after robotic *vs.* laparoscopic resection consistently demonstrates favourable outcomes for robotic surgery. A case-matched comparison between laparoscopic and robotic procedures revealed no change from baseline at one year, however the robotic group had significantly better erectile function within the first six months^[36]. Another comparative study supported these findings which found that male sexual function scores deteriorated across all components of the questionnaire in the laparoscopic group but not in the robotic group^[35]. Given this review of the literature, urinary outcomes are comparable between the groups, however the data favours robotic surgery for earlier return to baseline sexual function.

Learning curve

Transitioning from open procedures to minimally invasive techniques can be a daunting task for the surgeon. While both robotic and laparoscopic surgery are an entirely new skill set, it is postulated that the robotic platform facilitates this shift to modern surgical techniques. Patient outcomes and surgical efficiency are standard outcomes for measuring the learning curve for these operations. The literature supports a rather short learning curve for the robotic platform, as many surgeons are already experienced in laparoscopic surgery and quickly make the adjustment to robotics. A systematic review of the learning curve evaluated by operative times found a range of 5 to 310 cases for laparoscopic surgery (most were in the range of 35-50), and 15 to 30 cases for robotic surgery^[39]. Other studies also support a case volume of 50-80 laparoscopic *vs.* 20-50 robotic surgeries is necessary to attain proficiency^[10,40,41].

A unique study investigated the simultaneous learning curves of a surgical fellow/trainee by evaluating both laparoscopic and robotic right hemicolectomy operative times. The numbers of procedures required to identify a decrease in operative time was determined to be 16 for robotic surgery and 25 for laparoscopic surgery^[42]. There is evidence that surgeons with little to no laparoscopic experience can successfully transition directly to the robotic platform. Kim *et al.*^[43] compared two surgeons performing 100 rectal cancer cases, one of which had performed less than 30 laparoscopic procedures *vs.* a surgeon that had done over 300 laparoscopic surgeries. The inexperienced minimally invasive surgeon showed a marked decrease in operative time after 17 cases and had shorter operative times at the completion of the study without any difference in oncological outcomes compared to the seasoned laparoscopist. In conclusion, the learning curve for robotic surgery is faster than laparoscopy, and feasible for all experience levels.

CONCLUSION

Robotic surgery has gained widespread popularity for many reasons. Ergonomically, many surgeons prefer the robot console for comfort over the course of lengthy operations. Workplace overuse injuries specific to laparoscopic surgery can include neck, lower back, and wrist ailments, due to instrument handling and monitor positioning. The reported percentage of musculoskeletal disorders ranges from 73%-100% for laparoscopic surgery and 23%-80% for robotic surgery^[44]. Electromyography has been used to compare muscle activation between laparoscopic and robotic surgery, revealing that muscle activation was higher in most muscle groups in laparoscopic compared to robotic surgeons^[45]. The only muscle group that did not show significant difference in activation was the trapezius, and this was correlated to poor positioning of the robotic eyepiece. Lee *et al.*^[46] surveyed 432 exclusively robotic surgeons and reported that 56% of surgeons still have discomfort manifested by eye strain, neck stiffness, and finger fatigue, as well as lower back stiffness with increased surgical volumes.

This review of the literature clearly demonstrates both minimally invasive techniques to be equivalent in terms of meaningful perioperative outcomes, though intraoperative costs are consistently higher for robotic surgery. One must be careful when evaluating the data as there are many unmeasurable confounding factors that may affect outcomes. Conversion rates may be misrepresented in favour of robotic surgery if complicated cases with an anticipated high likelihood of conversion to open surgery were planned laparoscopically to save time docking the robot. Operative times may be misrepresented as none of the data evaluated teaching atmospheres and time given to the surgical trainee *vs.* the attending physician. The narrow length of stay differences may be affected by preoperative delays or postoperative transportation availability. Despite all these possibilities, the two platforms continue to show negligible differences that do not reach statistical significance in almost all studies. The robotic platform may boast a shorter learning curve, though it should be noted in many of these cases the surgeon already has laparoscopic experience performing the procedure and understanding the planes of dissection.

Much effort has been spent evaluating the difference between these platforms. However, the incision, extraction site, surgeon, and operation are the same, save for the advanced capabilities inherent in the robotic instruments. The ultimate decision on whether to perform robotic *vs.* laparoscopic surgery should be based on surgeon preference and familiarity with equipment, as well as local resources.

DECLARATIONS

Authors' contributions

Manuscript preparation: Kavalukas SL, Ghuman A, Sharp SP

Manuscript review and Editing: Wexner SD

Availability of data and materials

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Conflicts of interest

Dr Wexner is a paid consultant and receives royalties for intellectual property license from Intuitive Surgical, Medtronic, and Karl Storz and is a paid consultant for Stryker. all other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Nanomaterial-based hydrogels for coronary interventions: a mini review

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Abstract

Myocardial infarction (MI) has become a major health concern these days. Elevated levels of cholesterol due to improper diet cause severe damage to human health, resulting in the narrowing of blood vessels leading to MI. Different approaches have been used based on surgical and non-surgical treatments for these blockages to cure MI. In this regard, injectable and non-injectable hydrogel-based percutaneous coronary intervention has shown promising applicability for the treatment of cardiac damage and its repair. In this report, we summarize a few hydrogels based on natural polymers such as chitosan, alginate, polyethylene glycol and extracellular matrices to be used for percutaneous coronary intervention in the treatment of MI. Their structure, biological properties and biocompatibilities are discussed, and their existing challenges are also detailed. In addition, the probable solutions to overcome certain set backs are also highlighted.

Keywords: Myocardial infarction, percutaneous coronary intervention, hydrogels, biocompatibility, stents

INTRODUCTION

The heart functions regularly to recirculate the blood to the whole body. In general, the main function of the heart is to pump the oxygenated blood throughout the body. A breakdown in the functioning of the heart causes the irregular supply of oxygen to the organs and, consequently, can cause severe life-threatening effects such as heart failure, organ collapse and nerve damage, as well as the malfunction of



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various organs. In fact, cardiovascular diseases have been major fatal causes these days. Although recent advances in cardiac tissue engineering (CTE) such as stem cell therapy, artificial tissues and scaffold-based systems have emerged as powerful techniques for the treatment of coronary diseases, yet the developments of 3D printed scaffolds for the speedy treatment of the cardiac tissues are the demand of new era^[1]. The improper flow of blood may result in myocardial infarction (MI), i.e., heart attack, simultaneously causing damage to heart cells. This condition usually occurs due to blockage in one or more of the coronary arteries. The situation arises due to the accrual of fats and cholesterol in and on the artery wall known as plaque, which restricts blood flow. Thrombosis is mostly caused by the rupture of plaque, which is explained as the structural defect or gap in the fibrous cap. This exposes the highly thrombogenic core to the blood^[2]. The accumulation of these fats and cholesterol is known as atherosclerosis^[3].

Percutaneous coronary intervention (PCI) is one of the most used non-surgical procedure for the treatment of atherosclerosis. In brief, a thin flexible tube known as a catheter is used to place a small stent (structure) in the heart vessels to open up the blood capillaries, when narrowed by the plaque^[4]. Various materials have been utilized as a PCI tool for the treatment of MI. Soft material based hydrogels are being used in various forms in CTE^[5-7]. This complex research area is being explored by various interdisciplinary approaches involving material scientists, cell biologists, chemical biologists and nanotechnologists. Among these approaches, nanotechnology has played an extensive role in the biomedical section due to the tunable surface and material properties exploited for PCI. The surface-to-volume ratio, surface charge, and integration with the cells and proteins make nanomaterials highly effective in various fields of biomedical science, including CTE. The wide biomedical applications of nanotechnology include but are not limited to drug delivery^[8,9], tissue engineering^[10,11], hyperthermia^[12,13], and nanoantibiotics^[14-17].

Various nanomaterials have also been utilized for the designing of PCI, and are being explored for their practical applicability. These nanomaterials possess unique mechanical properties for their applications in PCI for the treatment of MI. A few of the most studied materials used for PCI are alginate^[7], chitosan^[18], polyethylene glycol (PEG)^[19] and extracellular matrix (ECM)^[20]. In this review, we mostly focus on these four materials as hydrogels for PCI applications. We discuss the structure, biochemical interactions, and applications of these materials for PCI referring to a few of the recent studies. Additionally, we discuss the future prospects of these materials to be utilized for CTE as well as in the treatment of the MI.

HYDROGEL-BASED CORONARY INTERVENTIONS

Hydrogels are chemically or physically cross-linked hydrophilic polymers, which possess effective mechanical as well as the chemical properties. These hydrogels are usually capable of absorbing biological fluids many times their weight, making them suitable for various biomedical applications. However, the major issue with hydrogels remains their toxicity to biological system. The residual monomer, cross-linker and catalysts cause the toxicity after the degradation of hydrogels^[21]. As discussed above, various material-based hydrogels have been utilized for applications in PCI. PCI-based strategies may help damaged cardiac tissues to recover; however, severe cases require the implantation of ventricular assist devices, creating an invasive method for the treatment. The advancements in this field are ongoing with interdisciplinary approaches for the PCI-based treatments. A few of the recent advances using alginate-, ECM- and PEG-based hydrogels and their salient features are listed in Table 1.

The stiffness of materials, bioactivity, and biodegradability are the key factors that play an important role in the selection of hydrogels for PCI^[30]. Nanotechnology in this regard provides an upper hand to the researchers to tune these properties by controlling the size, structure and morphology of the materials. However, each of these properties is crucial in the selection and rejection of the stent, yet the inherent properties of the material control the desired reactions. For example, the cross-linking of the materials controls the stiffness of the hydrogels^[19]. In addition, the swelling and the degradation behavior are also

Table 1. Recent advances in hydrogel-based PCIs in cardiac repair

S. N.	Materials	Major components	Salient features	Remarks	Ref.
1.	Alginate dialdehyde-gelatin hydrogel	Alginate and gelatin	3D orienting of cell-laden hydrogel Homogenous cell distribution High cell viability	Suitable for 3D printing in cardiac tissue engineering	[22]
2.	VentriGel	ECM from decellularized porcine myocardium	A first-in-man clinical trial of ECM-hydrogel Safe and feasible in post-MI patients with left ventricular dysfunction Improvements in left ventricular remodeling > 1 year and vice versa for < 1 year of treatment	Efficient for the treatment of post-early and -late MI	[23]
3.	Collagen-based hydrogel	Transglutaminase cross-linked gelatin	Stem cell-based therapy for ischemic heart disease Improved retention and cardioprotection Combination therapy may protect against cardiac injury after MI	Dual functionality, suitable for the treatment of MI and cardiac repair	[6]
4.	Thrombin-coagulated fibrin hydrogels	Decellularized ECM from porcine ventricular tissue and fibrinogen	Inclusion of cells due to thrombin 3D embedding enhanced cellular differentiation Recovery, frequency, synchrony and spontaneous beating	Suitable for cardiac cell differentiation	[20]
5.	Alginate/ECM hydrogel	ECM from porcine heart into alginate	Enhanced rheological and mechanical properties > 80% viability with > 100% metabolic activity Non-invasive delivery	Cell-free treatment of MI	[24]
6.	PEG-based injectable hydrogels	Triblock copolymers (PDEGMA-b-PPEGMA-b-PDEGMA)	A triblock polymer- formed gel Reversible sol-gel transformation 20 wt% formed strong gel in 5 seconds	Suitable as a scaffold for tissue engineering	[25]
7.	Polydopamine-containing hydrogel membrane coating over the metallic stent	Polydopamine-containing hydrogel membrane- and acrylamide	Stable coating for a non-invasive approach Improved HUVEC viability/proliferation and suppressed SMC viability Acrylamide enhanced mechanical strength	Non-invasive treatment of MI due to blockage	[26]
8.	H ₂ S releasing peptide hydrogel	Peptides FBA-IAVEE and FBA-IAVEEEE	Inhibited proliferation and migration of VSMCs Reduced intimal hyperplasia Proliferation of human umbilical endothelial cells	Suitable as a coating material for stents	[27]
9.	Hyaluronic acid hydrogel	Hyaluronic acid	Sustained miRNA-302 delivery by hydrogels Local clonal proliferation at injection within 2 weeks Decreased cardiac end diastolic and end-systolic volumes, with improved ejection fraction and fractional shortening	miRNA-based therapy for cardiac tissue engineering	[28]
10.	Silk fibroin microsphere-based alginate hydrogel	Alginate containing silk fibroin hydrogels	Sustained delivery of insulin-like growth factor 1 via hydrogel Reduction in infarct size within 28 days Improved cardiac function	Suitable for cardiac tissue engineering	[29]

PDEGMA: poly (diethylene glycol methyl ether methacrylate); PPEGMA: poly (polyethylene glycol methyl ether methacrylate); PCI: percutaneous coronary intervention; ECM: extracellular matrix; MI: myocardial infarction; SMC: smooth muscle cell; VSMCs: vascular smooth muscle cells; PEG: polyethylene glycol; FBA-IAVEE: 4-Formylbenzoic acid-(Isoleucine-Alanine-Valine-Glutamic acid-Glutamic acid); FBA-IAVEEEE: 4-Formylbenzoic acid-(Isoleucine-Alanine-Valine-Glutamic acid-Glutamic acid- Glutamic acid- Glutamic acid); HUVEC: Human umbilical vein endothelial cells

important for the working efficiency as well as the acceptance/rejection of the hydrogels as stents^[21]. Furthermore, various modifications have also been made on hydrogels for creating multi-functionality such as stent materials with imaging properties to track the exact location and the site of action^[31]. Similarly, various drug delivery applications of hydrogel-based materials have also been utilized in the treatment of the MI. Hence, the tunable properties for the site-specific applications make hydrogels materials very specific in the design as well as the applications. Recent developments using chitosan-, alginate-, PEG and ECM-based hydrogels for the treatment of MI are discussed in the upcoming sections.

CHITOSAN-BASED HYDROGELS FOR PCI

Chitosan is one of the most studied materials for the treatment of MI using PCI. Its cross-linking properties make it a promising candidate for creating 2D and 3D stents to be used for PCI. Chitin and chitosan (deacetylated derivative of chitin) are natural polymers and found abundant in nature (approx. 1000 t/year).

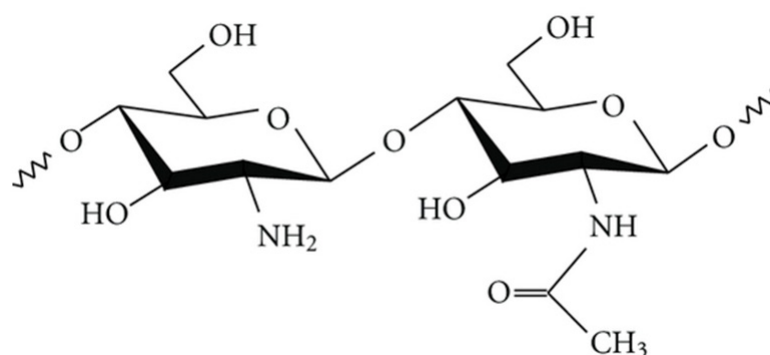


Figure 1. Chemical structure of chitosan, comprising *N*-acetyl-*D*-glucosamine (right) and *D*-glucosamine (left) units. Adapted with permission from Andrade *et al.*^[33]

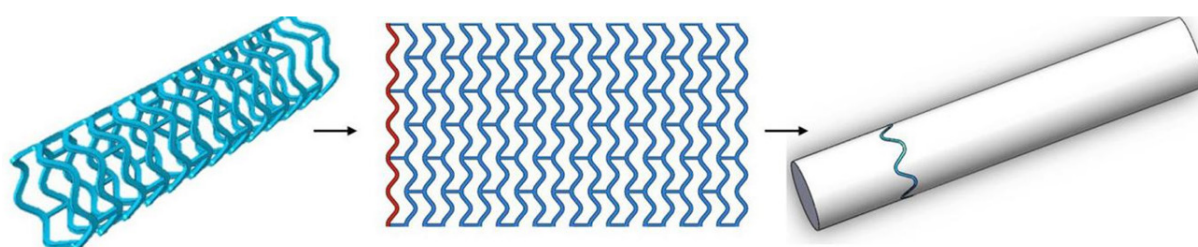


Figure 2. 3D-printing trajectory strategy of polycaprolactone stent. Adapted with permission from Qiu *et al.*^[35]

They are made up of randomly distributed β -(1-4)-linked *D*-glucosamine (deacetylated unit) and *N*-acetyl-*D*-glucosamine (acetylated unit)^[32] as shown in Figure 1^[33]. Most of their properties such as bioactivity, biodegradability, antibacterial activity and cellular adhesion depend on the degree of deacetylation and molecular weight^[9]. Besides, the amine groups present in chitosan provide the advantage of interacting with the cells as well as the cell adhesion proteins^[18]. However, cellular and enzymatic rejection of chitosan-based hydrogels is the major lag restricting their practical applications. Hence, cross-linking plays an important role in the biological response of chitosan.

Various approaches for the use of chitosan as a hydrogel for cardiac treatment, especially as a stent, have been made because of its tunable stiffness, wettability and swelling properties^[9,18]. It is well known that sulfated chitosan enhances the bioactivity of the material^[34]. In a recent study, Qiu *et al.*^[35] designed a 3D-printed bioresorbable stent using polycaprolactone (PCL), surface modified with sulfated chitosan. Chlorosulfuric acid (HClSO_3) was used to sulfonate chitosan at 70 °C. A polymeric tabular stent (diameter \times length: 3 mm \times 10 mm) of PCL was 3D-printed using the electrospinning technique, as shown in Figure 2. The mechanical properties of PCL stents were not compromised after modification with sulfated chitosan. No displacement was observed up to 0.7 N of force in either PCL- or sulfated chitosan-modified stent. Enzymatic degradation (wt%) was found to be 16% and 7% with and without lysozyme, respectively, after 60 days. These features indicated the suitability of the sulfated chitosan-modified stent for PCI applications.

In another study, Si *et al.*^[18] made a biopolymeric conductive hydrogel with conductive nano-dots. For this purpose, the authors prepared a chitosan/collagen hydrogel and combined it with graphene quantum dots (CS/CG-GQDs). Later, the designed hydrogel was impregnated with human mesenchymal stem cells (hMSCs), which resulted in improved angiogenesis and consequently decreased the cardiomyocyte necrosis caused by the hydrogel. The addition of conductivity, as well as hMSCs decreasing the death rate of cardiomyocytes, and the addition of GQDs, healed the fibrosis by altering electrical conductivity, leading

to the treatment of the cardiac tissues. A 3D porous network with pore size of $20 \pm 3 \mu\text{m}$ and $32 \pm 5 \mu\text{m}$ was respectively obtained for CS/CG and GQDs-CS/CG hydrogels. The designed hydrogel possessed enhanced cell survival rate and pro-angiogenic factors, making it suitable for CTE to treat acute MI. Both studies suggest that the addition of chitosan creates a stent free from various cellular and enzymatic rejection problems and rapid degradation, leading to a suitable stent-based angioplasty after acute MI.

Various other studies have been conducted using chitosan as hydrogel material for PCI. Chitosan, being highly bioactive, biocompatible and moderately biodegradable, has also been used as a coating material on various stents for the treatment of MI^[35]. In such an approach, Lin *et al.*^[36] coated polyvinyl alcohol (PVA) fibers with chitosan using the spray coating method, without sealing the meshes. PVA fibers were fashioned into braids using 16-spindle braider and cross-linked with glutaraldehyde to stabilize the interlacing points followed by spray coating with chitosan. Mesh sizes ranging from $0.20\text{-}0.35 \text{ mm}^2$ with a membrane thickness of $0.27\text{-}0.41 \mu\text{m}$ were obtained. Chitosan coating was reported to improve compression resistance. It was found that the chitosan-coated PVA stents were suitable for use in PCI because of their higher bioactivity and cytocompatibility (80% cell viability).

A blending approach has also been attempted to enhance the biocompatibility as well as the biodegradation of the stent material. In a recent study, poly-lactic acid/chitosan nanofibers were electrospun and loaded with paclitaxel as a coating material for the prototype polymeric stent. A single-nozzle electrospinning approach was utilized to make the fibrous stent. The chitosan concentration was varied from 3-9 wt%, and the drug loading concentration wt was varied from 40-120 wt% to obtain an optimum composite fiber. The physical encapsulation of the drug in the polymeric matrix without any chemical bonding was reported. The samples with the 40% and 60% drug loading displayed controlled drug release. An increase in chitosan concentration provided more homogenous fibers with smaller mean diameter, yet agglomeration was observed after 5% chitosan. Excellent cell viability ($> 90\%$) was observed up to 60% drug loading. However, a further increase in the drug concentration resulted in decreased cell viability. The cell viability was decreased to 50% at a drug concentration 80% due to the exceeding the cytotoxic limit^[37]. Hence, these findings suggested that chitosan-containing stents are very effective for use in stents for PCI.

ALGINATE-BASED HYDROGELS FOR PCI

Alginate, a natural polymer, has also been studied as a potential material for cardiac stents in the treatment of MI. Alginate possesses moderate cross-linking properties demonstrating it as a suitable candidate for stent preparation. Alginates are linear copolymers and are mostly composed of (1-4)-linked α -L-guluronic (G) and β -D-mannuronic (M) residues as shown in Figure 3. The number of sequences depends on the isolation species, i.e., the organisms and tissues. The random sequences of these G and M residues intercalate to form the alternating region of the MG blocks. The rigid 6-membered sugar rings add the restricted rotation around the glycosidic linkage and provide stiffness to the alginate^[38]. This indicates its suitability for stent applications, as stiffness similar to that of the artery is a required property of stent material for proper blood flow, restriction from mechanical damage and degradation.

Alginate has been utilized for various biomedical applications because of its gelling properties and natural origin. Cross-linking is usually done by the diffusion method using Ca(II) or Na(I) ions making the polymer stiffer^[39]. The inherent pre-requisite of cross-linking for the gel formation by alginate monomer makes it more effective and provides the competence to tune the stiffness for various applications. In addition, high mechanical and chemical stability, adequate swelling properties, narrow pore size distribution and pore size^[40] make alginate a strong candidate for stent formation. However, its poor bioactivity and biocompatibility, as well as its stiffness equivalent to the surrounding tissues, need to be explored prior to its application. Various approaches have been explored to use alginate as stent material for the treatment of MI using PCI. Recently, You *et al.*^[22] prepared an alginate dialdehyde-gelatin hydrogel bio-ink for 3D

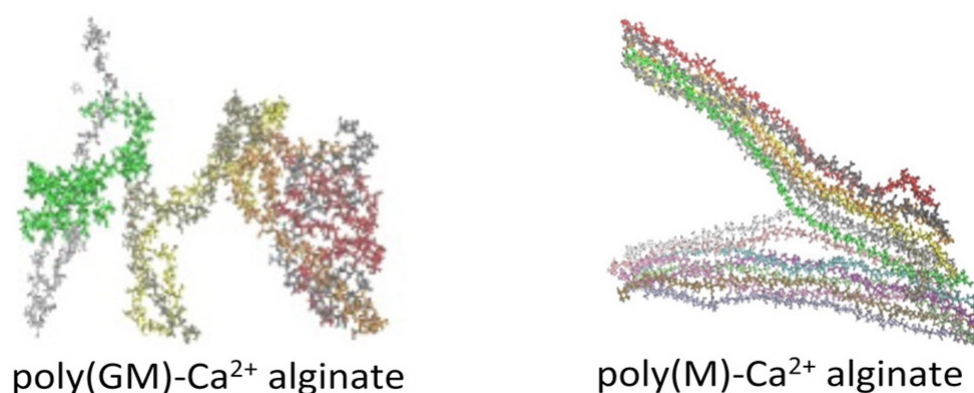


Figure 3. Chemical structure of alginate. G and M refer to α -L-guluronic and β -D-mannuronic residues, respectively. Reprinted (adapted) with permission from Hecht *et al.* [38]. Copyright (2016), American Chemical Society

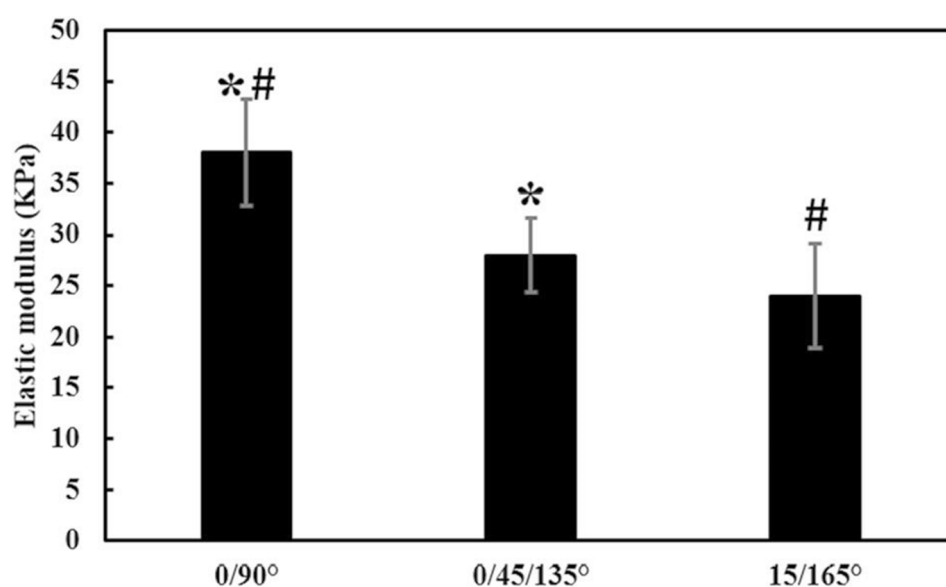


Figure 4. Elastic modulus of 10% alginate dialdehyde-gelatin hydrogels (70-30 wt%) with three angular designs: (1) each layer adhered to the underlying layer at 90° (0/90°); (2) the second layer adhered to the underlying layer at 45° and the third layer adhered to the first layer at 135° (0/45/135°); and (3) second layer adhered to the first layer (15°) at 165° (15/165°) (*, # $P < 0.05$). Adapted with permission from You *et al.* [22]

printing for the treatment of MI. The 3D bioplotter system was used for printing of the scaffolds. The authors claimed that 10% oxidation degree of 70 wt% alginate dialdehyde and 30 wt% gelatin concentration provided the best printability, making it suitable for the 3D printed scaffolds. The authors also seeded the living cells (EA.hy926) and demonstrated cell spreading as well as excellent cell viability up to 7 days. It was found that the above proportions provided the most homogenous cell distribution among the scaffolds with cell viability of > 90% after 7 days. In terms of mechanical properties, 0°/90° pattern showed the higher elastic modulus (~33 Pa) than that of 0°/45°/135° (~28 kPa) and 15°/165° (~24 kPa) patterns as shown in Figure 4. The scaffolds were found to be suitable for long-term application for CTE as well as the treatment of the MI. PCI using such bioinks provide a suitable stiffness, cell interaction and cell proliferation as well for biomedical applications. Similarly, Sack *et al.* [41] demonstrated that alginate hydrogel injections act as a suitable candidate in the treatment of MI as a left ventricular mid-wall constraint in swine. It was claimed that the hydrogel injection therapy moderated the elongation in sarcomere lengths from $1.78 \pm 0.15 \mu\text{m}$ to $1.68 \pm 0.10 \mu\text{m}$ after the treatment. In addition, systolic contractility (ejection fraction) was significantly

enhanced from $34.7\% \pm 2.7\%$ to $43.9\% \pm 2.8\%$. Moreover, the designed model showed realistic simulation with $> 99\%$ accuracy, when small myofiber strain in the nearby solidified hydrogel was kept at 13 mm away from the implant. These findings clearly showed that solidified alginate-based materials may mimic the mid-wall structure of the left ventricles, and can be used for various cardiac applications. Both of the latter studies showed the effective interaction of cardiac cells with alginate. Alginate hydrogels possess the required stiffness as well as the mechanical properties in comparison to cardiac cells, demonstrating them as one of the most suitable candidates for use in the treatment of MI.

In addition, there are various other properties that also make alginate a suitable candidate for use in the treatment of MI. Its non-toxicity to blood cells has been a keen objective for researchers. Various studies have been done on the blood cell toxicity of alginates. In this direction, Qi *et al.*^[42] studied alginate oligosaccharide for CTE and demonstrated its effect on the human platelet aggregation. A concentration-dependent inhibition of human platelet aggregation, clot retraction and spreading was obtained for the alginate oligosaccharide in the concentration range of 0.1-1.0 mg/mL. Similarly, ATP release was found to be concentration-dependent and was induced by thrombin and collagen formation. Bleeding time was found to be 534 ± 62 s in vehicle control and 581 ± 60 s in mice with alginate pretreatment. These findings demonstrated the blood compatibility of the alginate and its plausible applications in the treatment of MI. In addition, the blends of alginate with various materials have also been explored to obtain the desired biocompatibility for the biomaterial-based treatment of MI. In this regard, Curley *et al.*^[24] designed an injectable alginate/ECM hydrogel for the acellular treatment of MI. The storage modulus, compressive modulus and dynamic modulus for high G block alginate/ECM hybrid hydrogel at day 1 were found to be 1.6, 29 and 14 kPa, respectively. The excellent cell proliferation ($> 85\%$) with metabolically active cells ($> 100\%$) as compared to the control was obtained, proving the hybrid alginate-ECM system to be a suitable candidate for non-invasive treatment of MI. All these studies showed that alginate-based materials have excellent biological properties for CTE.

PEG-BASED HYDROGELS FOR PCI

PEG has been utilized for various biomedical applications because of their highly tunable size and orientations. PEG is a polyether compound based on its molecular weight. It is also known as polyethylene oxide or polyoxyethylene. PEG is considered a water-soluble, low immunogenic and biocompatible polymer. PEGylation expands the orientation as well as the size of the conjugated compounds, which consequently results in resistance to enzymatic digestion, making it suitable for various biomedical applications, including the treatment of MI^[43]. PEG has various properties that makes it an ideal candidate to be used as hydrogel material in PCI. Additionally, its different solvent-based orientations provide a tunability for various applications. For example, in hexadecane, it carries a well described freely jointed chain structure, whereas in water, a deformation in the supra-structure within the polymer has been observed, resulting in entropic to enthalpic elasticity^[44]. This restricts its water-based applicability in terms of mechanical properties and biocompatibility.

Various approaches have been examined to use PEG for PCI in the treatment of MI on the basis of its solvent-selective elasticity as well as water solubility. Recently, Boyacioglu *et al.*^[45] studied the shape memory behavior of PEG plasticized Polylactic acid (PLA)/thermoplastic polyurethane (TPU) blends. The shape memory behavior was investigated as a function of PLA/TPU ratio, plasticizer molecular weight and programming conditions. The plasticization efficiency was found to decrease with increase in molecular weight of PEG. It was claimed that with an increase in TPU content, the recovery ratio between 40-55 °C was also increased. However, at 60 °C for 20/80 PLA/TPU blends, the maximum total recovery ($> 80\%$) was obtained because of the strong elasticity of TPU. The shape memory values were found to be dependent on PEG molecular weight in a reverse order, and the blend was able to manage 245 kPa of stress, indicating its applicability for PCI in the treatment of MI.



Figure 5. Survival of rats; PEG-20k improves survival duration vs. PEG-20k with saline placebo vs. saline placebo with epinephrine. Adapted with permission from Ge et al.^[47]. * $P = 0.0022$ vs. PEG-20k with saline placebo; # $P = 0.0016$ vs. PEG-20k with Saline-A; † $P = 0.0005$ vs. PEG-20k with epinephrine; ‡ $P = 0.012$ vs. saline placebo with epinephrine. PEG: polyethylene glycol

In another study, Lin et al.^[46] prepared the PCL/PEG coated PVA biodegradable composite stents with a core-shell structure for various applications. The coated yarns were weft knitted into braids followed by thermal treatment, which resulted in a core-shell structure. In a typical process, the authors fitted the PVA yarns into a machine, followed by twisting, coating, and weft knitting. Different ratios (wt%) of PCL/PEG, i.e., 100/0, 90/10, 80/20, 70/30, 60/40, and 50/50 were melted and blended 5 times at various processing temperatures ranging from 70–100 °C at a step size of 10 °C. A coating machine was utilized to coat the PCL/PEG mixtures followed by heat treatment at 60 °C for 15 min to form the stents. The diameter of the composite stent was found to be 3 mm. The high PCL ratios, i.e., PCL/PEG 100:0 and 90:10 possessed the high porosities of 24.93% and 26.50%, respectively. Further increase in the PEG content from 20–30 wt% decreased porosity to 23.39% and 23.29%, respectively. This indicated that porosity increased up to 20% of PEG concentration and was decreased with further increase in concentration. This study clearly showed that porosity is a function of PCL/PEG concentrations. The synergistic effect on the thermal behavior of the composite was confirmed by the crystallization temperature ranging between that of PCL and PEG. The compressive strength of composite stents was found to be enhanced with an increase in PEG concentration up to 30% (6.15 N) and decreased with a further increment (4.5 N). The maximum cell viability was also observed at 30% PEG concentration, i.e., > 90%, and decreased with a further increment (~40%), indicating a correlation between mechanical properties, PEG concentration and cell viability as well. This study helps to understand the effects of PEG concentration on cell attachment as well as the mechanical properties required for the use of PEG for designing the stents. Ge et al.^[47] examined the effects of aortic-infused PEG-20k during cardiopulmonary resuscitation on various cardiac functions. An increase in coronary perfusion pressure to the same extent as with epinephrine resulted in an improvement in the post-resuscitation myocardial and cerebral functions and inhibition of cardiac arrest. The *in vivo* studies showed that four rats survived in the PEG-20k groups, zero rats in the saline-placebo and only 1 rat survived after > 24 h in the epinephrine group, as shown in Figure 5. The studies explain that the cardiac functioning of the PEG-based material depends on its structure, molecular weight and orientation as well. Similarly, Aykar et al.^[48] manufactured the self-standing microfluidic chip using PEG-diacrylate (PEGDA)-based hollow microvessels with inner dimensions of 15–73 μm. The macromer solutions were focused onto a single microchannel hydrodynamically and were subsequently solidified through photopolymerization. The emphasis was to mimic the arteries (0.1 mm to > 1 cm), arterioles (10–100 μm), capillaries (4–12 μm),

venules (10–100 μm), and veins (0.1 mm to > 1 cm). The optimized wt% for a balance in mechanical strength and cytocompatibility was found to be 50% of PEGDA. All these studies have proven PEG as a special candidate with highly tunable cell response, mechanical strength, bioactivity and cell functioning as well. PEG can be tuned on the basis of its molecular weight, orientation and cross linking with other materials as well. PEG is mostly blended with existing materials such as PCL to synergistically enhance the desired properties for PCI in the treatment of MI.

ECM HYDROGELS IN CARDIAC TISSUE REPAIR

The cardiac ECM is made up of three major components, namely glycoproteins, proteoglycans, and glycosaminoglycans. Various glycoproteins such as fibronectin, laminin, fiber proteins, and prototypical matricellular proteins enrich the cardiac ECM. The major protein in cardiac ECM is fibrillar collagen. In mammalian hearts, cardiomyocyte proliferation may occur in neonates at a cardiac injury, but in adults, regeneration capacity is absent^[49]. Cardiac ECM has a prominent effect in cardiac repair and regeneration, and changes vigorously after MI^[50], yet the mechanical stiffness of free ECM is a major challenge in its use for PCI. Various approaches have been developed on the basis of ECM being used directly as the biomaterial for the cardiac tissue repair. ECM molecules are isolated and utilized directly as injectable hydrogels by intramyocardial injection or intracoronary perfusions. In these approaches, the injectable materials were supplemented with various materials such as DNA/RNA and cell active factors along with cardiac cells and growth factors as well, as shown in Figure 6, which synergistically helped in the repair of the cardiac tissues^[51].

In a recent study, Du *et al.*^[52] investigated the role of 5A/6A promoter polymorphism in the matrix metalloproteinase 3 (MMP-3) gene and in-stent restenosis (ISR). An increment in the ISRs with genotype proportion of 6A6A and a decrement in the 5A allele were reported. The findings suggested the role of gene-based cell proliferation in ISRs, hinting at the role of ECM interaction with the stents in cardiac tissue repair. Similarly, MMP-2 and -9 also play an important role in acute MI and cardiac tissue repair^[53]. Hence, addition/delivery of these proteins may play a pivotal role in designing PCI with effective cardiac tissue repair. Growth factor impregnated nanomaterials play a vital role in CTE. In this direction, Mewhort *et al.*^[54] proposed a surgical procedure using a CorMatrix-ECM biomaterial patch for the treatment of ischemic heart failure. The electrocardiography revealed an increment in the ejection fraction of basic fibroblasts, and prevention of left ventricle remodeling. The improvement in left ventricle contractility was confirmed by the pressure volume loop analysis. Various other factors such as coating of ECM and its biodegradation have also been tested for the improved healing/repair of the damaged cardiac tissue. In this regard, Liu *et al.*^[55] performed the nanocoating of ECM-Inspired SDF-1 α /Laminin for cardiac wound healing on the 316L stainless steel surface, as shown in Figure 7. It was found that the biomolecules were delivered in a controlled way at the site of action, and a promising approach was established to repair the cells after the injury. In addition, the designed layer inhibited platelet adhesion and activation, leading to controlled or reduced thrombosis and clot generation. The designed layer also enhanced endothelial cell migration and endothelial progenitor cell aggregation, resulting in faster cardiac tissue repair. All these studies showed that the incorporation of ECM and its constituents significantly affected the cellular repair and has a promising future if clubbed with PCI in the treatment of MI.

CHALLENGES AND FUTURE PERSPECTIVES

Various approaches have been applied in the treatment of MI using hydrogels with a varied degree of success. These approaches have been individually focusing on various factors such as mechanical strength, reduced thrombosis, tissue repair and cell regeneration. However, very few approaches have been attempted to incorporate all the desired properties in single stents to be used for PCI in the treatment of MI. Additionally, the hydrogels for PCI possessed major challenges in their mechanical strength,

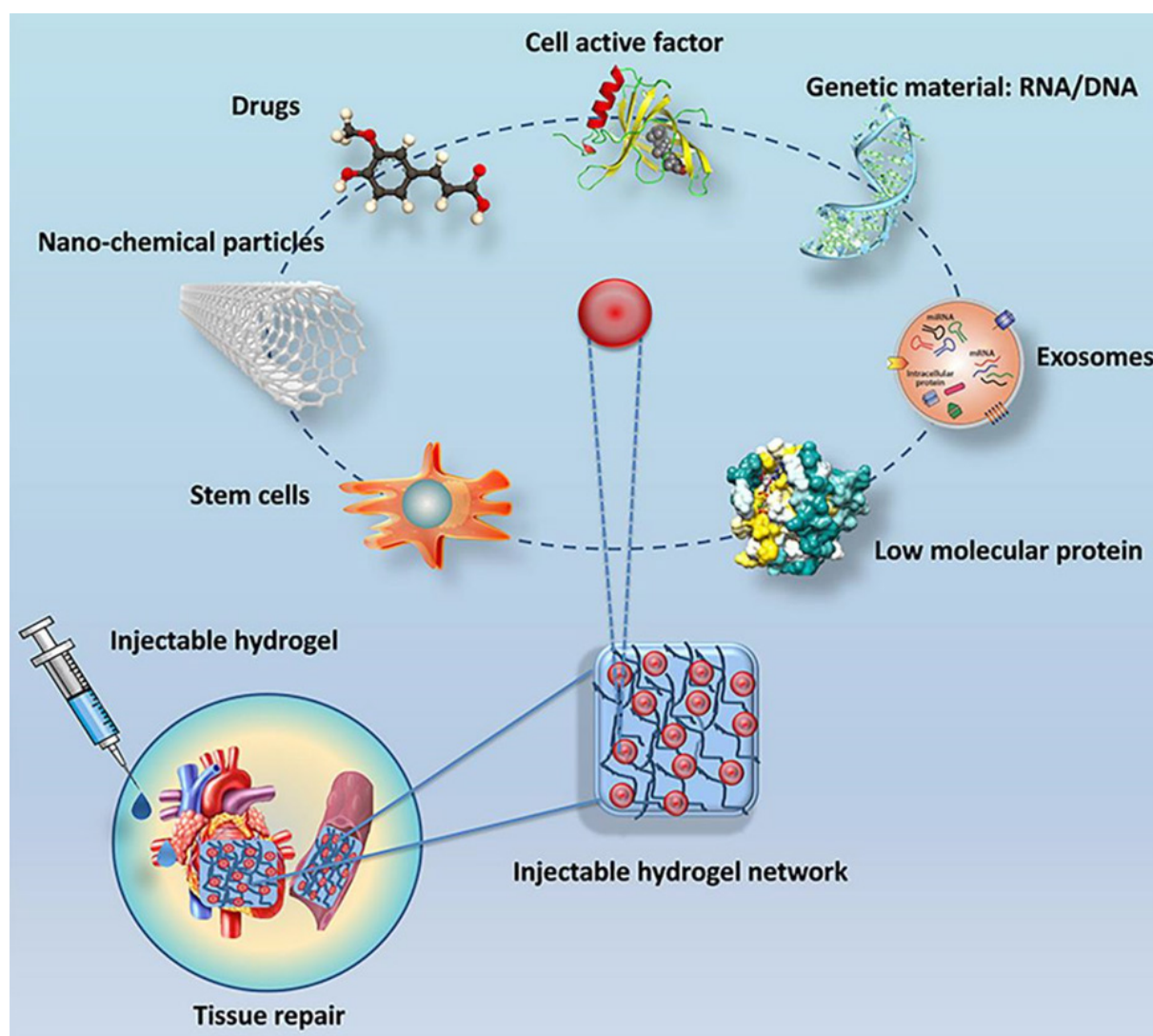


Figure 6. Representation of cardiac tissues using hydrogels, cardiac cells and growth factors. Adapted with permission from Liao et al.^[51]

biodegradation, bioactivity and host body responses. Various hydrogel-based materials are being studied at the preclinical and clinical levels to be used for PCI. The selection of polymeric material is usually based on its cross-linking ability, interfacial interactions and enzymatic degradation^[56]. These selections are usually based on the: (1) endogenous repair system of the host body leading to the challenges in mimicking of mechanical strength of the surrounding tissues; (2) the indigenous structure of polymers leading to the challenges in responses of cells and proteins; and (3) the salvage of the degraded polymeric debris leading to the challenges in enzymatic degradation. Hence, the major challenge remains to incorporate all these desired properties in a single stent, i.e., selection and/or design of a material with excellent bioactivity without compromising its mechanical strength and enzymatic degradation. In this direction, the chitosan- and alginate-based hydrogels have shown excellent properties in terms of their mechanical strength, biodegradability and cellular responses; however, their cytocompatibility solely depends on the degradation rate as well as degradation products. The monomers are usually non-toxic to cells^[32], but the polymeric debris with specific orientation and their pharmacokinetic profiles affect the blood vessels and other body tissues as well^[57]. Similarly, PEG-based materials have shown promising cell attachment and cardiac cell regeneration capacity but lack in biodegradation and also cytocompatibility. PEG is usually considered an antifouling agent^[58], and doesn't allow the non-specific adhesion of protein and cells. These properties

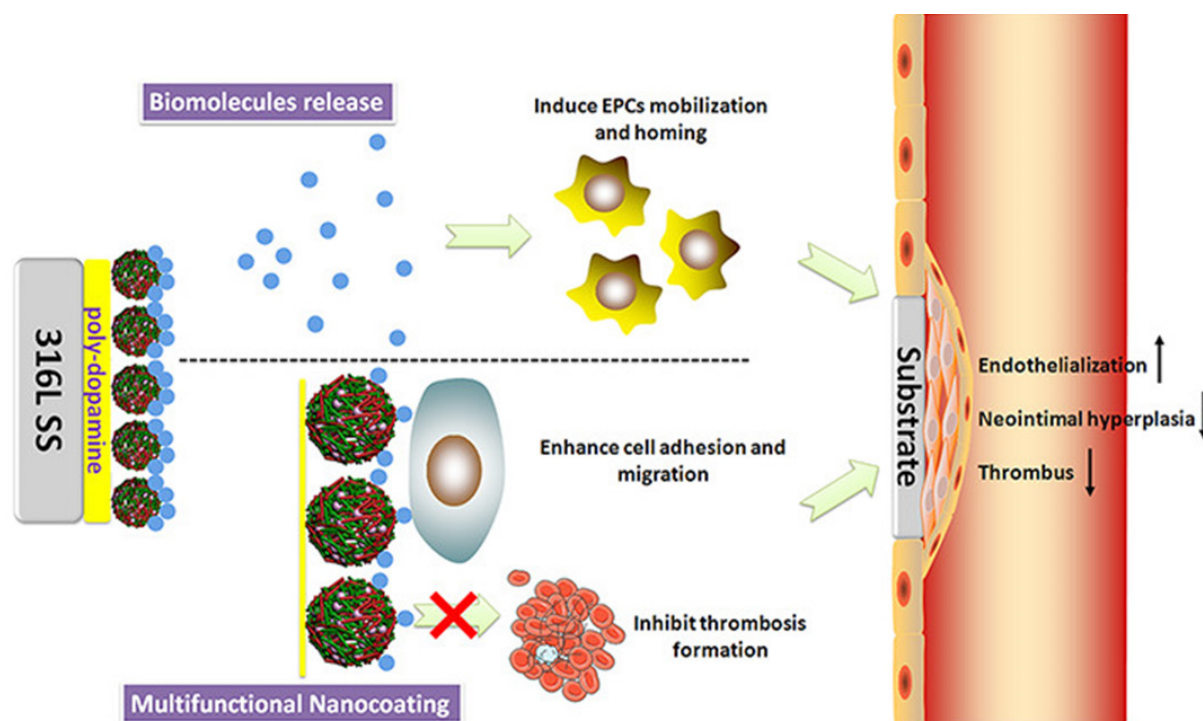


Figure 7. ECM-inspired nanocoating over stainless steel with enhanced wound repair. The modified surface effectively prevented thrombosis formation by inhibiting platelet adhesion and activation, while accelerating endothelial cell adhesion and migration. The controlled delivery of biomolecules induced the immobilization of EPC. Reprinted (adapted) with permission from Liu *et al.*^[55]. Copyright (2017), American Chemical Society. EPCs: endothelial progenitor cells; ECM: extracellular matrix

can be utilized to coat it over stents for antifouling properties. ECM-based materials are considered the best tool for cardiac tissue repair; however, their poor mechanical strength limits their use alone for the synthesis of stents for PCI.

The drawbacks of these materials can be removed by blending them with each other or by creating a composite material of these fractions. In Section “ECM HYDROGELS IN CARDIAC TISSUE REPAIR”, it was seen that various growth factors and genes may provide excellent tissue repairability. Hence, nanomaterials based on chitosan, alginate and PEG can be impregnated with these ECM molecules. The delivery of these ECM materials can be tuned by controlling the molecular weight as well as the orientation of the composite structure. The cross-linking within the hydrogel and its respective mechanical strength and biodegradability can also be tuned. These approaches are advised to obtain site-specific materials for the designing of hydrogels for PCI. For example, the composite polymeric hydrogels can be designed to tune their mechanical strength as well as enzymatic degradation. One promising method is the construction of layer by layer structure for the stent material impregnated with ECM, which may provide the controlled release of ECM biomolecules and controlled biodegradation of the amalgamated materials. The composite material can also improve the enzyme-based degradation of the stents and reduce thrombosis. Furthermore, supplementation of cell cycle inhibitors, e.g., Rb1 and Meis2 and stem cells have been applied to engineer the cardiac tissue after MI. These approaches can be utilized to add biofunctionality to the hydrogels for the treatment of MI^[59,60].

In addition, clot degrading agents such as heparin-based delivery system compiled with the stent hydrogels also seem to be an important tool in CTE^[61]. Not much work has been done in this direction, but it can lead to a multifunctional stent material. Another drawback of hydrogel-based stent materials is their inability to kill bacteria, causing severe detrimental effects including immunogenic responses such as inflammation,

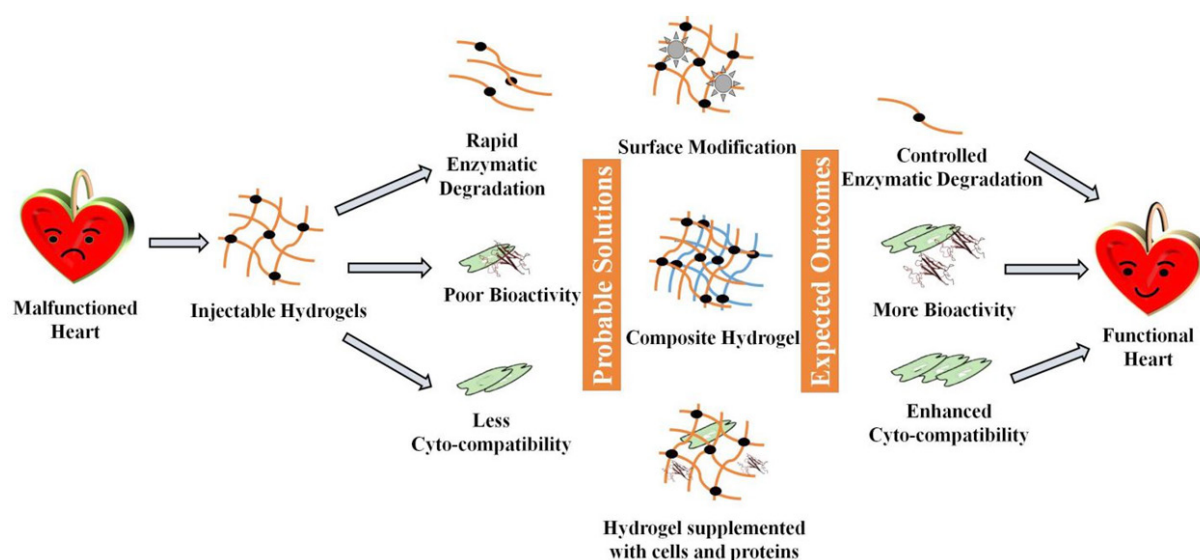


Figure 8. The major challenges of hydrogels, probable solutions and expected outcomes for the treatment of myocardial infarction

arterial disruption, and hemorrhage^[62]. Few of the materials have been modified with Ag NPs and drugs to enhance the antibacterial activity of chitosan and other polymers^[9,10], but their application in stents has not been tested. Various peptide and peptoid materials have shown promising antibacterial activity^[16,63,64] and can be incorporated in stent materials for PCI. Various surface-engineered drug delivery systems have been explored with excellent antibacterial and drug-releasing properties^[65]. These approaches can be linked with hydrogels to bring the multi-functionality of drug release, mechanical stiffness and cardiac tissue repairing in stent materials. Target deficiency, i.e., the inability to be targeted at the site of action and biocompatibility are the major issues in biomaterial research. Recently, the effects of amine, octyl and mixed groups for surface modifications on protein attachment, orientation and cell adhesion have been scrutinized^[66-68]. This strategy may be implemented to modify the surfaces of the stents for better protein interaction, biocompatibility and improved interfacial interactions as well. Interdisciplinary approaches may provide a better solution for cardiac tissue repair and reduce the harmful after-effects of MI. The major challenges of hydrogels, probable solutions and expected outcomes are depicted in Figure 8.

CONCLUSION

CTE is being extensively studied these days. Improper blood flow and damage to cardiac tissues are the major causes of MI. The blockages in blood vessels are the major factors that lead to MI. Various surgical and non-surgical studies have been performed to relieve the blockage in the coronary vessels, including PCI. Soft polymeric materials are constructed in the form of hydrogels, which are molded for making the stents to broaden the vessels for proper blood flow. Hydrogel-based materials have shown promising ability to be used for PCI; however, lack of the required mechanical strength, bioactivity and enzymatic degradation limits their practical applications. The controlled orientation of polymeric materials with specific bioactivity along with controlled enzymatic degradation has been major challenges for biomaterial researchers. There have been recent advances in the self-degrading hydrogel stents based on chitosan, alginate, PEG and various other polymeric materials. These materials have shown promising results at the laboratory scale to be utilized for PCI in the treatment of MI. Owing to their native properties, these materials have overcome many of the lags in PCI; however, they lack multi-functionality. Hence, interdisciplinary approaches to design a composite of these individual polymers blended with ECM biomolecules are proposed to develop promising materials for hydrogel-based stents in the treatment of MI.

DECLARATIONS

Authors' contributions

Performed data analysis and interpretation: Saxena V

Writing - original draft, review and editing: Saxena V, Pandey LM

Conceptualization, draft designing, formal analysis, supervision: Pandey LM

Availability of data and materials

Not applicable.

Financial support and sponsorship

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Standardized definitions and concepts of radicality during minimally invasive thymoma resection

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Abstract

Radical thymectomy is the gold standard treatment for thymoma; in particular, completeness of surgical resection of a well-encapsulated thymoma and adequate margins are considered the most important prognostic factors. According to the International Thymic Malignancy Interest Group instructions, in fact, the thymus should be resected *en bloc* with its upper cervical poles and the surrounding mediastinal fat and through a *no-touch* surgical technique. For years, the open approaches have been considered the gold standard treatment for thymic masses, because of technical advantages and proved good oncological results. When applied to properly chosen patients on the basis of the tumor stage, dimension, and histology, minimally invasive approaches could be as effective as open ones in terms of long-term outcomes. To accomplish a minimally invasive thymoma resection, several minimally invasive techniques (transcervical, subxiphoid, thoracoscopic, and robotic) have been described, each presenting advantages and drawbacks. Moreover, when dealing with early stage neoplasms, many authors have proposed to perform the thymomectomy alone, not involving the rest of the thymic gland, but evidence is still imprecise and vague, and some studies have described a higher rate of local recurrence when using this technique. Finally, many studies suggest that surgeons with expertise in minimally invasive lymphadenectomy for lung cancer may easily endorse the idea of nodal dissection, to be performed at least in advanced thymomas involving neighboring structures, large masses, and thymic carcinomas.

Keywords: Thymoma, thymectomy, minimally invasive techniques, radicality



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INTRODUCTION

Thymic neoplasms and malignancies are relatively uncommon. Approximately 90% of the tumors of the thymus are thymoma, accounting for about 0.2%-1.5% of all cancers. The remaining 10% are thymic carcinoma, carcinoid tumors, or lymphomas. Indications for thymectomy include suspected thymoma, myasthenia gravis (MG) with and without thymoma, and thymic cysts^[1-4].

Radical thymectomy is the gold standard treatment for thymoma; in particular, completeness of surgical resection and adequate margins are considered the most important prognostic factors^[5,6]. Complete surgical resection of a well-encapsulated and noninvasive thymoma is usually curative, with low risks of local recurrence^[7]. Invasive thymoma and thymic carcinoma could be treated with multimodal therapy including induction or adjuvant chemo- or chemoradiotherapy associated with *en-bloc* surgical resection. Surgery is also indicated for treatment of local recurrences and, in some cases, pleural and pericardial implants^[8]. To achieve the most complete surgical resection, the International Thymic Malignancy Interest Group (ITMIG) has suggested two surgical procedures for patients with or without MG [Table 1], respectively: extended thymectomy, including the *en bloc* removal of the contiguous right and left mediastinal pleura, mediastinal, and pericardiophrenic fatty tissues, and dissection of aorta-pulmonary window, in addition to complete thymectomy [Figure 1] or complete thymectomy, including the *en bloc* removal of the upper cervical poles and the surrounding mediastinal fat [Figure 2]^[9].

Along with the *en bloc* resection of thymoma, a no-touch surgical technique should be performed; the thymoma, in fact, should not be grasped or squeezed with retractors because of the possible rupture of the capsule with subsequent pleural dissemination, as Kamel *et al.*^[9] demonstrated. Moreover, areas of potential tissue disruption should be marked immediately during dissection on both the specimen and the patient^[10]. Completeness of thymectomy should be assessed by macroscopic inspection of the thymic bed, specimen, and subsequent pathological analysis^[11]. Complete resection (R0) is defined when there is no evidence of residual tumor (macroscopically and/or microscopically) while incomplete resection is defined when there is evidence of microscopically (R1) or macroscopically (R2) residual tumor. When dealing with thymomas, there is often little tissue surrounding the tumor and quite often the capsule itself constitutes the outer surface of the specimen, leading to misleading interpretations of the margins [Figure 3].

In such cases, only through-and-thorough penetration of the capsule by tumor which reaches the outer surface should be interpreted as a positive margin^[12]. After an R0 resection or a complete radiographic response has been previously achieved and an adequate 5-10 years of follow up has been carried out, recurrence can be defined^[10]. Given the indolent behavior of many of these tumors, ITMIG has suggested that freedom-from-recurrence (FFR), as calculated from the date of resection to the date of first recurrence, is a better measure than survival in patients who have successfully undergone curative treatment^[13]. Average recurrence rates are low for Masaoka Stage I tumors (3%) but increase progressively to 11% and 30% for Stage II and III tumors, respectively^[14].

For years, the optimal surgical approach, combining the best degree of resection with minor surgical invasiveness, has been discussed^[15-18]. Minimally invasive approaches have become increasingly relevant in the last two decades and a proved alternative to open techniques, which are still considered the gold standard treatment because of technical advantages and proved good oncological results^[19]. According to the above-mentioned general principles about radical thymectomies, ITMIG guidelines^[10] have been proposed for minimally invasive resections. They should involve no rib spreading or sternal cutting, dissection, and visualization of innominate vein, both phrenic nerves, and pleura in the case of suspected invasion. Moreover, the access incision for retrieval should be large enough to prevent specimen disruption; retrieval should always be done in the bag; and a correct examination of the removed specimen to assess for completeness of the resection is required^[10].

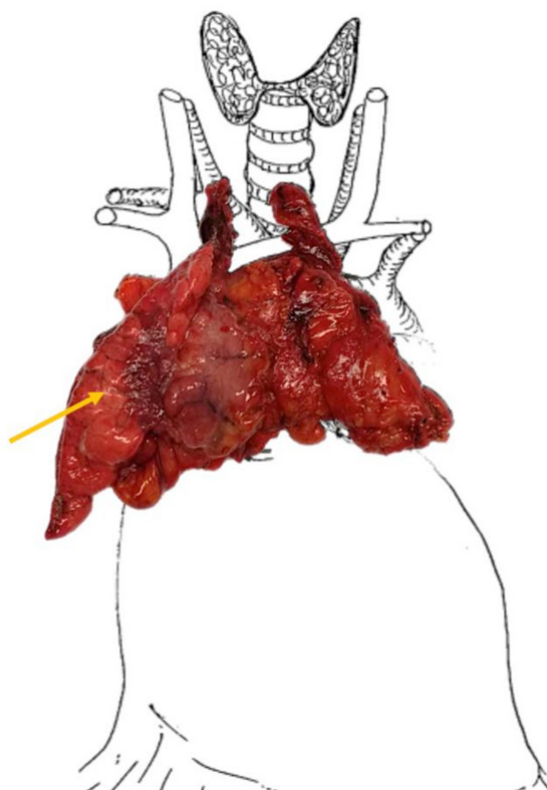


Figure 1. Thymic specimen after *en bloc* resection for locally advanced thymoma invading the lung (indicated with yellow arrow)



Figure 2. A: Gross specimen after completed video-assisted thoracic surgery thymectomy including all adjacent fat; B: the gross cross section revealed a thymoma 2 cm in size

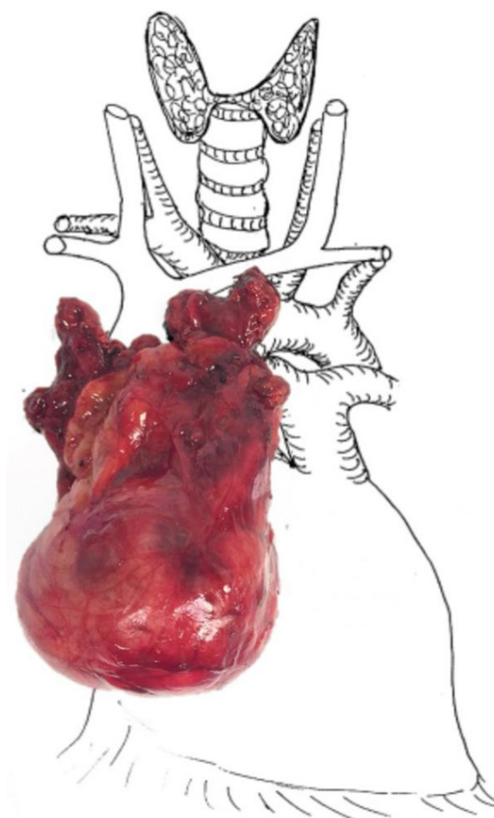


Figure 3. Gross specimen after resection of a well-circumscribed thymoma with a thin fibrous capsule

Table 1. Comparison between extended thymectomy and completed thymectomy

	Extended thymectomy	Completed thymectomy
Indication	Thymic mass MG Both	Thymic mass MG Both
Preoperation preparation	CT/MRI Neurological evaluation for detection of MG Plasmapheresis or immunoglobulins in myasthenic patient	CT/MRI Neurological evaluation for detection of MG Plasmapheresis or immunoglobulins in myasthenic patient
Resection extent	Removal of thymus, thymic fat and other mediastinal structures infiltrated by the mass (pericardium, lung, etc.)	Removal of the grossly identifiable thymus and variable amounts of anterior mediastinal fat
Postoperative care	Extubation if good respiratory effort and blood gases Close control of vital signs, especially saturation Aggressive pulmonary toilet Early ambulation Anticholinesterase agents if weakness occurs Plasmapheresis in case of respiratory standpoint worsening Drainage removal in case of patient stability	Extubation if good respiratory effort and blood gases Close control of vital signs, especially saturation Aggressive pulmonary toilet Early ambulation Anticholinesterase agents if weakness occurs Plasmapheresis in case of respiratory standpoint worsening Drainage removal in case of patient stability

MG: Myasthenia Gravis; MRI: magnetic resonance imaging; CT: computed tomography

The correct indication of the surgical approach in thymic lesions should be chosen on the basis of the tumor stage, dimension, and histology^[20]. Cheng *et al.*^[21] suggested that patients would be suitable for minimally invasive thymectomy by fulfilling some radiological criteria: location of the tumor in the anterior mediastinum, tumor encapsulation, presence of a distinct fat plane between the tumor and surrounding structures, existence of residual normal appearing thymic tissue, no mass compression effect, and unilateral tumor predominance, particularly for tumors larger than 3 cm [Figure 4].

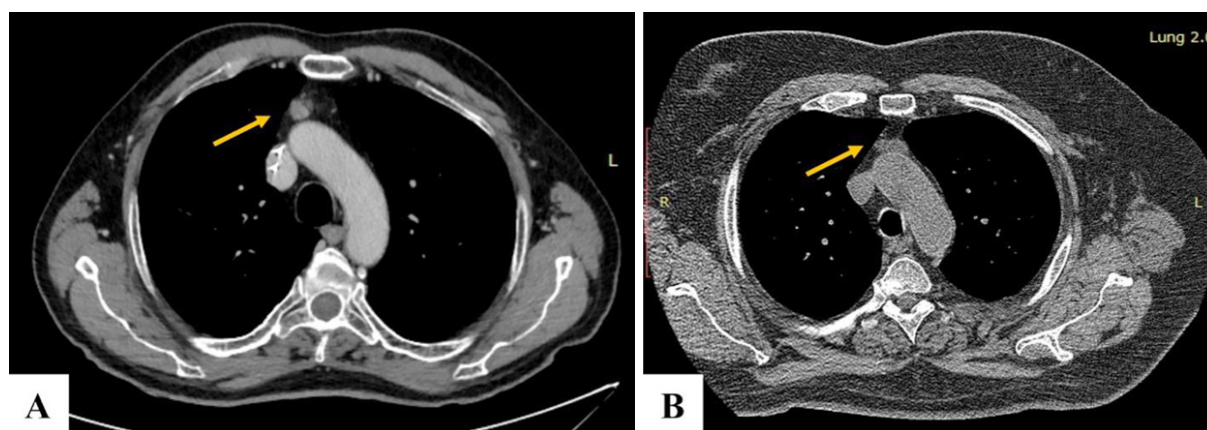


Figure 4. A, B: Computed tomography scan images showing two small thymomas, one (A) with typical calcifications, with regular outlines, amenable to minimally invasive surgery. Histology was positive for type A thymoma (Masaoka-Koga Stage I)

Most published studies agree that thymic lesions larger than 5 cm should be excluded from the minimally invasive approach; to date, dimension is not considered an absolute contraindication, but big lesions may interfere with the thoracoscopic procedure, forcing a conversion, prolonged operative time, and capsule injuries^[22]. Kimura *et al.*^[23] reported that tumor capsule injury during video-assisted thoracic surgery (VATS) is observed more frequently in patients with thymomas > 5 cm and the recent Japanese Alliance for Research in Thymoma (JART) study found statistically more recurrences in patients with thymomas > 5 cm^[24].

Perforation of the capsule, incomplete resection possibility, *en bloc* resection not achievable, and disruption of the tissues exposing the tumor could compromise the complete oncological resection, and they force conversion to open^[10,25].

Several minimally invasive techniques (transcervical, subxiphoid, thoracoscopic, and robotic) have been described to accomplish a minimally invasive thymoma resection, each having advantages and drawbacks.

VIDEO-ASSISTED TRANSCERVICAL THYMECTOMY

The transcervical approach for thymectomy was first reported by Sauerbruch in 1912^[26] and then performed by Crile in 1966 in a series of patients with myasthenia gravis^[27] and by Kirschner and Kark in the 1970s^[28,29]. It was only in 1988 that Cooper and colleagues^[30] reported a modified approach to perform and extend transcervical thymectomy in contrast with the limited technique reported earlier. Extended thymectomy involved use of a sternum-lifting and a self-retaining retractor to improve mediastinal exposure allowing a more complete removal of mediastinal thymic tissue and extrathymic fat. With the spread of new technologies and minimally invasive approaches, in 1993, the thoracoscopic approach for thymectomy was described for the first time^[31]. The advantages of the video-assisted transcervical thymectomy are those of a transcervical route: lower morbidity and pain, shorter hospitalization, faster patient recovery, and reduced cost^[32]; moreover, the uniportal transcervical route obviates entry into the pleural spaces, negates the need for chest tubes, provides enhanced exposure in the neck region, and a split-lung anesthesia via a double-lumen endotracheal tube is not mandatory. It is an efficient and inexpensive procedure with a one-night hospital stay and minimal postoperative pain and discomfort to the patient^[33]. Relative contraindications to a transcervical approach include prior mediastinal surgery and/or irradiation and cervical spine disorder limiting extension of the neck^[33]. The main concerns about this technique are about the narrow surgical field leading to instrument crowding and the not complete visualization of the thymus with the subsequent impossibility to perform a complete clearance of the mediastinal fat compared to an open surgery.

During the years, to surpass these limits, some modified and combined approaches have been described. Ampollini *et al.*^[34], for example, described a modified video-assisted transcervical approach, which, using the instruments developed for the minimally invasive thyroidectomy, enable the surgeon to perform the thymectomy without neck hyperextension or permanent sternum elevation, which are mainly responsible for postoperative pain. Yu *et al.*^[35], instead, proposed a combined transcervical and unilateral-thoracoscopic thymectomy approach to reach the residual thymic tissue, which might have been left behind in the superior horns or in the upper poles into the base of the neck.

SUBXIPHOID THYMECTOMY

The subxiphoid approach was introduced in 1999 by Kido *et al.*^[36], paving the way for Hsu *et al.*^[37], who first performed subxiphoid video-assisted thoracoscopic extended thymectomy in 2002. Since then, the subxiphoid approach has been used successfully and many techniques have been described according to the incision design: the uniportal or dual-port subxiphoid approach^[38-40], the subxiphoid and subcostal arch approach, subxiphoid robotic thymectomy^[41,42], and a combination of the transthoracic and subxiphoid approaches^[43].

Each technique should be chosen on the basis of the personal preference of the surgeon along with his experience and of the single case to treat, according to its anatomical peculiarities^[44]. Although the uniportal approach seems to be the most minimally invasive approach in existence, it is not an easy technique to learn because of the reduced instrument maneuverability; however, in skilled hands, this limit could be overcome with specially modified instruments and angled thoroscopes^[45,46]. Since the increase in the number of the ports can help obtain a multidirectional view, increasing the safety of the procedure, single-port thymectomy should be started following the training of two- or three-port thymectomy^[47]. The subxiphoid robotic approach is the one with the best maneuverability: the left and right robot arms are inserted in the 6th intercostal space, and the entire target/thymus lies between the left and right arms, thereby enabling maximum robot performances^[42].

The advantages of the subxiphoid approach are numerous; since the camera is inserted into a subxiphoid incision in the midline of the body, the surgical field is comparable to that in a median sternotomy. This helps identify the location of the bilateral phrenic nerves and confirm the location of the superior pole of the thymus while offering a good visualization in the neck area and a safe dissection of thymic veins^[42]. Other advantages include minimal postoperative pain with no occurrence of intercostal neuropathy since intercostal spaces are not traversed and cosmetic outcomes are excellent^[43,44,48]. In contrast, when comparing the subxiphoid view to the lateral one in the traditional VATS, it becomes difficult to identify the contralateral phrenic nerve, and there is also the risk of intercostal nerve injury, resulting in postoperative chronic incision pain^[43,49]. Zhang *et al.*^[43] recently conducted a retrospective analysis comparing 98 patients who underwent a VATS thymectomy through the subxiphoid and subcostal arch approach or the lateral intercostal one. They found statistically significant differences in the length of hospital stay, postoperative pain, and cosmetic satisfaction in favor of the subxiphoid approach.

To deal with larger thymomas and difficult selected cases, some modified approaches have been described. In their experience, Zieliński *et al.*^[16] proposed a “maximal” transcervical subxiphoid video-thoracoscopic thymectomy, in which, at the same time, two teams work from above and below the sternum to dissect the thymus while using a double sternal elevator. This technique has the advantage to be more extensive in regard to the removal of fatty tissue from the aorta-caval groove and fatty tissue anterior to the trachea, almost reaching the level of tracheal bifurcation. On the other hand, even if the two-team approach helps to reduce the operative time, it is a far more invasive technique than unilateral VATS affected by more complications than traditional VATS.

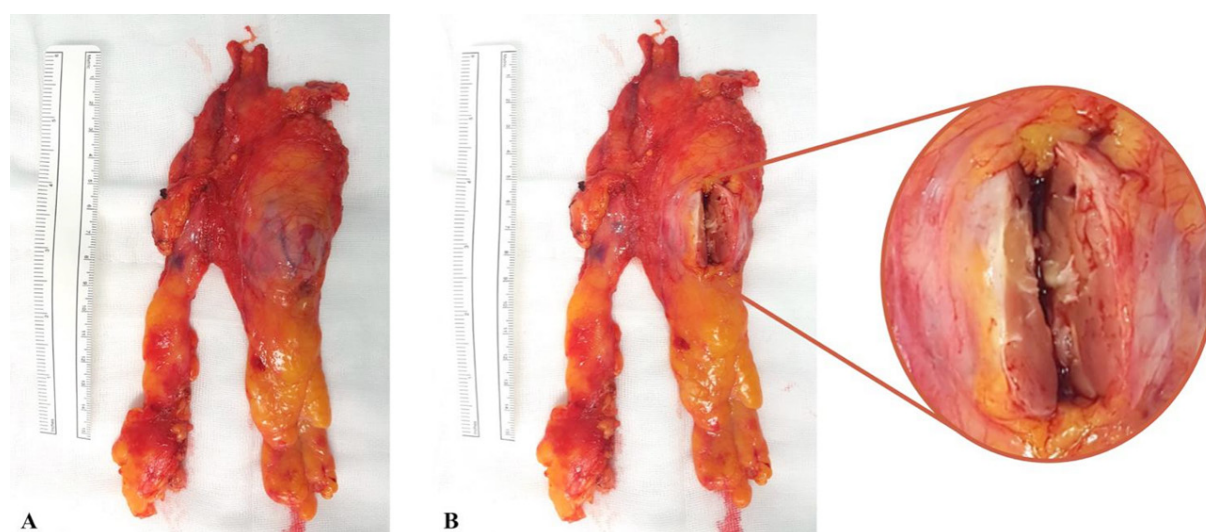


Figure 5. A: Gross specimen after *en bloc* video-assisted thoracic surgery thymectomy; B: gross cross section revealing a thymoma 3.5 cm × 3 cm in size (the zoomed-in nodule is shown in the circle)

Aramini *et al.*^[49] described the subxiphoid thymectomy approach aided by a double sternum retractor to better visualize the mass at the level of the anterior mediastinum, particularly in patients with large invasive tumors. The double sternum retractors provide the surgeon with a better view of the tumor, improving the surgical technique and thus preserving the principles of surgical radicality related to the surgical margins.

VATS AND ROBOTIC-ASSISTED THORACOSCOPIC SURGERY THYMECTOMY

VATS was introduced in the 1990s; since then, it has totally changed thoracic surgeons' approach to surgery. The advantages of minimally invasive techniques (MIT) compared with conventional open approaches are well known: shorter hospital stay, quicker recovery, better aesthetic result, lower perioperative morbidity, minor surgical access trauma, postoperative pain, and better preservation of pulmonary function. Despite this, the use of MITs in thymic surgery is still controversial. The main surgeons' concerns relate to the higher risk of rupture of the capsule with the consequent spread of tumoral cells, increased risk of local recurrence, and reduced safety margins [Figure 5].

Although recent studies have reported similar oncological outcomes for early-stage thymoma resections performed both by open and minimally invasive approaches^[50-53], the first one remains the gold standard treatment^[19]. This is because evidence is sparse and mostly deriving from case reports or retrospective studies due to the low incidence of these tumors. Moreover, given the indolent behavior of many thymic tumors, an adequate 5-10 years of follow-up should be carried out to establish the exact FFR and overall survival. Currently, few data about long-term follow-ups have been published and therefore statistics are still ineffectual.

No tremor filter, two-dimensional view of the operative field, and inability of the instruments to articulate are well-known VATS limitations, and they make it difficult to operate in such a rigid and tiny space as the mediastinum. The development of robotic technologies has solved some of the above-mentioned problems, allowing a better and safer surgical technique. The robotic system, in fact, is endowed by a three-dimensional, high resolution vision camera that enables the best possible view of the operative site; moreover, every endoscopic procedure around anatomic structures is easier and safer because the surgical EndoWrist can articulate and rotate 360 degrees with seven degrees of freedom articulation. These features make robotic surgery extremely appropriate for thymic surgery, enabling the surgeons to do a safe and



Figure 6. Gross specimen after *en bloc* video-assisted thoracic surgery thymectomy

comfortable dissection of vascular and nervous structures and a better dissection in remote, fixed, and difficult to reach areas of the neck and mediastinum^[11,53-57] [Figure 6].

The main limitations of robotic surgery are the high initial costs, the lack of tactile feedback, and the need of a large enough volume of patients to overcome the initial learning curve.

O'Sullivan *et al.*^[58] recently published a meta-analysis on robotic versus open and video-assisted thoracoscopic surgery approaches for thymectomy, including 18 articles. When comparing robotic *vs.* open thymectomy, evidence shows no differences in operative time, intraoperative complications, and mortality. On the other hand, significantly lower blood loss, fewer postoperative complications, shorter length of hospital stay, and decreased positive margin rate were reported in the robotic group. When comparing robotic *vs.* VATS thymectomy, instead, the results show no differences in the two groups in terms of operative time, blood loss, length of hospital stay, intraoperative complications, and margin rates. To date, few authors have performed a real comparison between the two techniques, considering not only the perioperative results but also long-term follow-ups [Table 2].

Perioperative parameters were analyzed by Qian *et al.*^[68]; when comparing 123 patients with early-stages thymoma who underwent robotic-assisted thoracoscopic surgery (RATS), VATS, or open thymectomy, they found significant differences in blood loss volume, mean postoperative pleural drainage duration, and duration of hospital stay. When comparing two groups for parameters, they found that the outcomes of RATS were more favorable than those of VATS and median sternotomy, while outcomes for VATS

Table 2. Best evidence papers about minimally invasive thymectomy

Ref.	No. of patients	Surgical approach	Thymectomy/ thymomectomy	5-year survival rate (%)	RR (%)	Mean follow up (months)
Roviaro <i>et al.</i> ^[59]	22	uVATS	Thymectomy	95	1.3	51.7
Cheng <i>et al.</i> ^[21]	44	uVATS	Thymectomy	100	0	36.4
Agasthian and Lin ^[60]	119	uVATS	Thymectomy	100	3.4	58.8
Pennathur <i>et al.</i> ^[61]	18	bVATS	Thymectomy	100	0	27
Takeo <i>et al.</i> ^[51]	35	bVATS	Thymectomy	100	2.8	65
Mussi <i>et al.</i> ^[62]	14	Robotic	Thymectomy	100	0	14.5
Marulli <i>et al.</i> ^[22]	79	Robotic	Thymectomy	97	1.3	51.7
Kimura <i>et al.</i> ^[23]	45	uVATS	Thymectomy	100	6.7	-
Marulli <i>et al.</i> ^[54]	100	Robotic	Thymectomy	100	0	67
Tseng <i>et al.</i> ^[83]	95	VATS (22)	Thymectomy (42) Thymomectomy (53)	100	4.5 1.5	57
Schneider <i>et al.</i> ^[63]	20	Robotic	Thymectomy	100	11.1	26
Liu <i>et al.</i> ^[64]	76	uVATS	Thymectomy	100	2.6	61.9
Ye <i>et al.</i> ^[65]	125	uVATS	Thymectomy	100	0	16.9
Keijzers <i>et al.</i> ^[66]	37	Robotic	Thymectomy	100	2.7	36
Bae <i>et al.</i> ^[82]	342	VATS (119) Transversal (1) RATS (1)	Thymectomy (239) Thymomectomy (103)	99 100	12.1 9.7	94.5 85.6
Gu <i>et al.</i> ^[80]	1,047	VATS (277)	Thymectomy (220) Thymomectomy (57)	93 96	3.1 5.4	38
Nakagawa <i>et al.</i> ^[81]	1,286	VATS (169)	Thymectomy (276) Thymomectomy (276)	97.3 96.9	4 1.8	53
Narm <i>et al.</i> ^[79]	762	VATS (297)	Thymectomy (76) Thymomectomy (72)	97 96.3	4.1 3.7	49
Marulli <i>et al.</i> ^[11]	134	Robotic	Thymectomy	100	0.7	48
Rusidanmu <i>et al.</i> ^[77]	118	VATS (unspecified)	Thymectomy (43) Thymomectomy (75)	88.4* 98.7*	6.98 2.67	-
Weng <i>et al.</i> ^[67]	358	VATS	Thymectomy	94.5	8	60.5

*10-year survival rate. RR: recurrence rate; RATS: robotic-assisted thoracoscopic surgery; VATS: video-assisted thoracic surgery; uVATS: uniportal VATS; bVATS: biportal VATS

were more favorable than those of sternotomy. Similar findings were reported by Şehitogullari *et al.*^[69]. In a recent analysis, they compared 21 vs. 24 patients who underwent RATS or VATS thymectomy. They found significant differences in terms of mean operative time, length of hospital-stay, and duration of pleural drainage, while mean operative time, operative pain, and remission rates were superimposable. Rückert *et al.*^[70] performed a retrospective analysis on 74 vs. 79 patients with MG who underwent robotic or thoracoscopic thymectomy. With a follow-up of 42 months, they found a significant difference in cumulative complete remission rate of MG between the two groups in favor of the robotic one (39.25% vs. 20.3%, $P = 0.01$); no differences were found in terms of conversion rate, operative time, and postoperative complications.

Burt *et al.*^[71] recently performed a retrospective multicenter analysis on 943 patients who underwent MIT or open thymectomy by focusing on R0 status as the primary outcome. By comparison, they found a non-significant difference in the R0 resection rate for patients treated with minimally invasive or open approach (83.4% vs. 79.4%), stating that the probability of achieving R0 resection for early-stage thymoma is not influenced by a minimally invasive approach, and MIT is equivalent to OT in this regard. Kamel *et al.*^[72] published a recent multi-institutional analysis on 2,558 performed thymectomies using an open, VATS, or RATS approach. They found that patients who underwent thymectomy via an open approach were younger, had more advanced tumors, had more incomplete resections (32% vs. 30%, and 23%; $P = 0.013$), less frequently underwent regional lymph node dissection, and had longer hospital stays compared to the VATS and robotic groups. When they performed a matched analysis, all those differences became not statistically significant and the three approaches resulted superimposable.

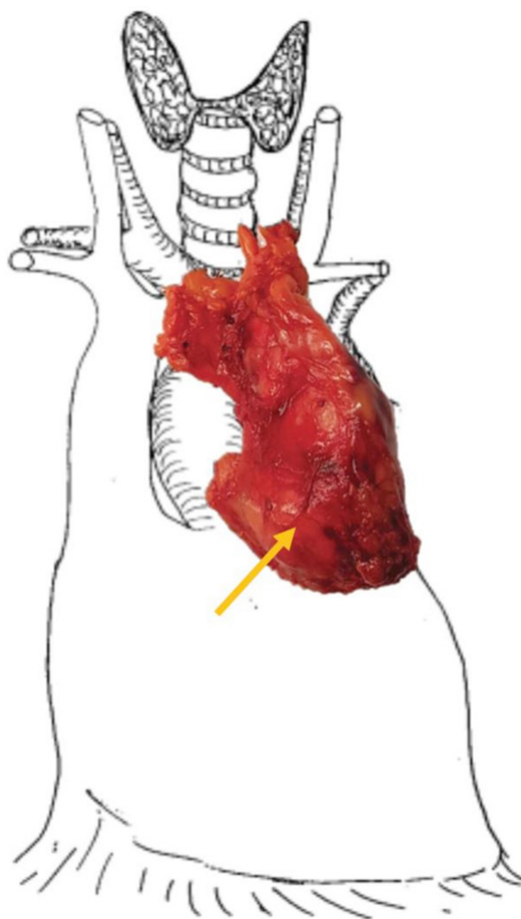


Figure 7. Gross specimen after robotic-assisted thoracoscopic surgery thymomectomy performed for a small intracapsular thymoma (yellow arrow)

Therefore, all published studies do not solve the doubts about which approach should be better among all the available ones and, thus far, no prospective randomized trials have been performed to clear them. For this reason, the choice should be done by the surgeons on the basis of both available evidence and surgeons' personal skills and preferences.

RADICALITY: THYMECTOMY OR THYMECTOMY?

All guidelines and large retrospective review studies recommend the complete *en bloc* thymectomy as the current gold standard in all resectable thymic lesions because of the risk of a multicentric thymoma development, the occurrence of MG after the operation, and the prevention of the local recurrences^[10,73-76]. However, many authors have proposed the resection of the thymoma without the rest of the thymic gland as a feasible and safe resection in early stage thymomas (Stages I and II) without MG^[77-86] [Figure 7].

Fiorelli *et al.*^[87] recently published the best evidence about equivalence in terms of oncological outcomes of thymomectomy and thymectomy in patients with early stage thymoma. They found ten papers, and most of which showed no statistical differences in terms of local recurrence, while differences were described in terms of surgical outcomes (operative time, blood loss, drainage duration, and hospital stay) in favor of the thymomectomy.

Among these studies, the largest multicentric ones^[80,81] were those with a proved higher rate of local recurrence in the thymomectomy group than in the thymectomy one. Gu *et al.*^[80], in their multicenter

study from the Chinese Alliance for Research in Thymoma database, retrospectively analyzed 1,047 patients who underwent thymectomy or thymectomy for early stages thymoma; they found a higher recurrence rate in the thymectomy group, especially for patients with Stage II thymomas (14.5% *vs.* 2.9%, $P = 0.001$). Similarly, Nakagawa *et al.*^[81], in their multicenter study from the JART database, retrospectively analyzed 1286 patients who underwent thymectomy or thymectomy for early stages thymoma before and after propensity score analysis; they found a higher recurrence rate in the thymectomy group (2.1% *vs.* 0.41%, $P = 0.06$).

Masaoka^[88] published an anecdotal study about his surgical experience in Osaka and Nagoya. In the first experience, most of the 93 patients underwent simple thymectomies, whereas a majority of patients in the Nagoya series underwent extended thymectomies; in the early 1980s, simple thymectomy was the procedure of choice, later replaced by extended thymectomy. He found that overall survival rates of the Nagoya series were superior to those of the Osaka one (87.1% *vs.* 66.7% for Stage I; 80.6% *vs.* 60.0% for Stage II).

Voulaz *et al.*^[89] published the first study about 157 patients who underwent thymectomy or thymectomy, comparing for the first time long-term outcomes for advanced-stage thymomas and carcinomas, while previous reports have focused only on early stages. They found that oncologic outcomes in terms of disease-free survival rate of thymectomy *vs.* thymectomy were superimposable and their median follow-up was 77 months.

To date, there is no prospective study comparing the two approaches and the evidence is still sparse, deriving from retrospective, single-institution, and small studies. The largest published analyses prove that thymectomy alone is not enough from an oncological point of view for early-stage thymoma. Moreover, given the indolent behavior of these tumors, long-term follow-ups are needed to assess the real rates of recurrence and the superiority of one technique to another.

LYMPHADENECTOMY

For many years, the role of lymphadenectomy of the mediastinum for thymic lesions has not been made clear, and this surgical procedure has long been underperformed. Despite this, lymph node metastases have proven to be a significant, independent, and adverse factor for FFR in patients with thymic carcinoma and thymoma. To date, no clear guidelines are available regarding lymph node dissection and data from the majority of studies show that lymph node sampling is not routinely performed during surgeries, except in Japan where lymphadenectomy has traditionally been a part of the thymic resection.

The Masaoka staging system included N involvement in Stage IVb but made no distinction among the different nodal stations^[88]. The eighth edition of tumor, node, and metastasis classification for thymic tumors, instead, has classified nodal stations into anterior (N1) and deep (N2) regional nodes; their involvement stage lesions as IVa or IVb disease^[90].

Anterior mediastinal lymph nodes seem to be the primary drainage basin for thymic epithelial tumors and lymphatic diffusion apparently spreads from the anterior to the deep nodes following a right route. This has been determined based on frequency and pattern of metastasis in addition to anatomical location: nodal metastases are located in the anterior mediastinum in 90% of thymomas and carcinoids and 70% of thymic carcinomas^[91].

The actual incidence of lymph node metastasis has not been well established. Historically, the prevalence of lymph nodes involvement has been described ranging from 1.8% to 5.1% in thymomas and from 20% to

33.5% in thymic carcinomas and NETs, but these rates could be underestimated because lymphadenectomy is rarely performed by most institutions^[91-95].

Two factors have been described to explain lymph node metastasis, namely WHO subtype and tumor size, being both closely related to the biologic aggressiveness of the tumor^[96,97]. Hwang *et al.*^[92] described lymph node metastasis rate according to WHO histologic types as 5% for Type A, 1.6% for Type AB, 4.8% for Type B1, 9.5% for Type B2, 10.7% for Type B3, and 31.8% for thymic carcinoma. They also found that lymph node metastasis rate was higher in tumor larger than 6 cm. Moreover, most authors have reported lymph node metastasis to be more frequent in tumors invading adjacent organs; these findings suggest lymph node dissection to be performed at least in those patients undergoing *en bloc* resection of thymus and neighboring organs for carcinomas and carcinoids^[97,98].

Park *et al.*^[98] suggested dissection of more than 10 lymph nodes to be enough for adequate staging. They retrospectively reviewed 45 patients who underwent thymic resection for carcinoma; during the surgery, they performed lymphadenectomy of a mean of 9.4 lymph nodes and divided the patients in four groups according to the extension of lymph node dissection: no lymph node dissection (Nx), node-negative by < 10 nodes dissection (N0a), node-negative by > 10 nodes dissection (N0b), and node metastasis (N1). They found that the five-year FFR rates were 33.3% in N1, 64.1% in N0a, 75% in Nx, and 90% in N0b, while the five-year DFS rates were 33.3% in N1, 48.1% in N0a, 75% in Nx, and 90% in N0b.

Although no evidence has proved it yet, it is possible that surgeons with expertise in minimally invasive lobectomy and lymphadenectomy for lung cancer may easily endorse the idea of nodal dissection, to be performed at least in advanced thymomas involving neighboring structures, large masses, and thymic carcinomas.

CONCLUSION

Radical *en bloc* thymectomy including the upper cervical poles and the surrounding mediastinal fat is the gold standard treatment for non-MG thymoma and adequate margins are considered the most important prognostic factors.

Open approaches remain the gold standard treatment, but minimally invasive techniques could be effectively used in small, early-stages thymic masses, above all because, despite the shortage of studies, the rate of radicality would seem to be slightly higher for minimally invasive techniques. Transcervical, subxiphoid, thoracoscopic, and/or robotic approaches have been described and compared in many studies, each having advantages and drawbacks. However, the lack of prospective randomized trials still gives no answer about which approach should be better among the available ones. Moreover, the concept of radicality should include pathological features of surgical removal (resection must involve the thymoma, thymus, and mediastinal fat) and operation modalities: minimally invasive resection of a thymic neoplasm does not require the use of rib retractor or the execution of sternotomy. The goal is to perform a complete resection using a video monitor, and the service incision to remove the neoplasm must be large enough not to damage the operating piece during extraction. Therefore, minimally invasive surgery is to be preferred to open techniques not only in terms of radicality but also for the best postoperative performance (less pain and aesthetic result).

Although several authors have proposed thymomectomy as a valid limited resection technique, appropriate for patients with small and early-stages thymomas, still little evidence supports its oncological and long-term advantages.

Finally, the role of lymphadenectomy of the mediastinum for thymic lesions has not been clarified, and this surgical procedure has long been underperformed. Since WHO subtype, tumor size, and invasion of

neighboring organs have been proved to often be associated with lymph node metastasis, evidence suggests that nodal dissection should be performed at least in advanced thymomas, large masses, and thymic carcinomas.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: De Iaco G, Brascia D, Marulli G

Performed data acquisition, as well as provided administrative, technical, and material support: Geronimo A, Sampietro D, Fiorella A, Schiavone M, Panza T, Signore F

Drafting of the manuscript: De Iaco G, Brascia D, Marulli G

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Systematic Review

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Minimally invasive pancreaticoduodenectomy with venous resection: results of a systematic review

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Abstract

Aim: Growing experience with minimally invasive pancreaticoduodenectomy (PD) has led surgeons to expand the indications for this approach. We systematically reviewed the literature on minimally invasive PD with venous resection.

Methods: The EMBASE, MEDLINE, and Cochrane central databases were systematically searched for articles from January 2010 to January 2020 describing cases of PD with venous resection. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The primary outcomes were feasibility and conversion rate. Secondary outcomes were morbidity, mortality, blood loss and 1-year survival.

Results: The literature search found 9 studies reporting 140 patients undergoing PD with venous resection. Sixty-six PDs were performed robotically (47.1%). The conversion rate ranged from 0% to 55%, blood loss ranged from 200 to 842 mL, and operative time ranged from 397 to 518 min. There were 82 lateral (58.5%) and 18 segmental (12.8%) PDs with venous resection. One patient had an associated arterial resection (0.7%). A graft was used for venous reconstruction in 28 patients (20%). Eight deaths (5.7%) were reported postoperatively.

Conclusion: Minimally invasive pancreatectomies with synchronous lateral venous resections are increasingly reported by highly experienced surgeons in high-volume institutions. Further experience is needed to validate this approach and prove its advantages over open surgery.



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Keywords: Pancreatectomy, vascular resection, venous resection, arterial resection, locally advanced tumours

INTRODUCTION

Since the first description in 1994 by Gagner and Pomp, minimally invasive (MIS) pancreaticoduodenectomy (PD) has been considered among the most complex abdominal procedures^[1]. Even if the feasibility and safety of the minimally invasive approach of MIS PD has been demonstrated in several randomized and observational studies, reluctance still exist to embrace MIS for PD^[2-5]. PDs are in fact a complex procedure entailing (1) extensive dissection around the mesenteric and coeliac vessels; (2) dissection above and below the mesocolon (multi-quadrant procedure); (3) a long and a technically challenging digestive reconstruction; and (4) inherent morbidity and mortality which seems not reduced by the MIS approach.

For these reasons, the MIS approach to PD is still not widely practised compared with other procedures such as colonic and gastric resection. However, increased experience with laparoscopy and robotics in surgery has allowed pioneer centres to test the feasibility and safety of these approaches for more advanced procedures. In fact, from a theoretical point of view, the magnified view provided by the laparoscope and/or the 3D vision achieved by robotics can be of great help during the dissection. This enhanced view, coupled by the superior dexterity of the robotic instruments, can be of great help in complex suturing.

Indeed, complex procedures such as renal or splenic artery aneurysm repair, nephrectomy with caval thrombectomy, and kidney and pancreas transplantation have been described in recent years^[6-11]. As a result of these developments and the increased experience achieved with MIS PDs, small series of MIS pancreatectomies with vascular resection have been reported^[3,5,11-19]. The safety and results of this approach remains to be determined. In this article we systematically reviewed the literature on the topic of MIS PD with vascular resection, evaluating the safety and feasibility as well as the outcomes of this approach.

METHODS

Data selection

The EMBASE, MEDLINE, and Cochrane central databases were systematically searched for articles from January 1995 to January 2020 describing cases of PD with venous resection. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and it was limited to manuscripts written in English. The following were used as search terms: “pancreaticoduodenectomy” combined with “laparoscopic” and/or “robotic” and “vascular resection” and/or “venous resection”. Potentially eligible articles were screened, and exclusion criteria included: (1) duplicated articles; (2) articles that were not in English or that described animal studies; and (3) registry studies for whom the patient outcomes could not be precisely detailed. References of selected articles were checked for additional cases. The primary outcomes of the review were feasibility of PD with venous resection. Secondary outcomes were morbidity, mortality, blood loss and 1-year survival. All the data were extracted using a standardized extraction form.

Statistical analysis

Continuous data are expressed as the mean \pm standard deviation or the median and range as appropriate, whereas categorical variables are presented as numbers and percentages. Differences between groups were assessed by the chi-squared or Fisher's exact test (categorical variables) and the Wilcoxon rank sum test or the student's *t* test (continuous variables).

Table 1. Outcomes of minimally invasive pancreaticoduodenectomy with vascular resection

Author	Year	Approach	Conversion	Blood loss (mL)	Operative time (min)	Venous resection	Lateral/segmental	Graft	Arterial resection	Mortality	Morbidity	Reoperation	Survival
Giulianotti <i>et al.</i> [16]	2011	Robotic	0	200	392	2	2/0	1 (PTFE)	0	0	1	1	NA
Groome <i>et al.</i> [14]	2015	Laparoscopic	0	842	465	31	22/9	12 [Patch (10), LRV (1), Synthetic (1)]	1	1 (3.3%)	11 (35.5%)	NA	75%
Boggi <i>et al.</i> [11]	2016	Robotic	NA	NA	NA	14	NA	NA	0	2 (14.2%)	NA	2 (14.2%)	NA
Khatkov <i>et al.</i> [18]	2017	Laparoscopic	NA	NA	NA	8	5/3	3 (1 Patch, 2 Prothesis)	0	1 (12.5%)	NA	1 (12.5%)	NA
Stauffer <i>et al.</i> [5]	2017	Laparoscopic	11	250	518	20	NA	NA	NA	NA	NA	NA	NA
Dokmak <i>et al.</i> [15]	2018	Laparoscopic	0	437	397	4	4	4	0	0	0	1	50%
Cai <i>et al.</i> [13]	2018	Laparoscopic	3	435	547	10	NA	2	0	0	40%	NA	NA
Beane <i>et al.</i> [12]	2019	Robotic	5	275	419	50	49/1	6 (Bovine pericardial patch)	0	4 (8%)	14 (28%)	1 (2%)	NA
Rosso <i>et al.</i> [19]	2020	Laparoscopic	0	150	435	1	0/1	0	0	0	1	0	NA

PTFE: polytetrafluoroethylene; LRV: left renal vein; NA: not available

RESULTS

The initial search resulted in 58 studies. Only 9 studies (reported from US, $n = 4$; France, $n = 1$; Italy, $n = 2$; Russia, $n = 1$; China, $n = 1$) matched the inclusion criteria, however [5,12-19] [Table 1, Figure 1]. This included 140 patients undergoing PD with vascular resection. Sixty-six PDs were performed robotically (47.1%). There were 82 laterals (58.5%), 18 segmental (12.8%) and 29 not specified venous resections (20.7%). One patient had an associated arterial resection (0.7%). Nineteen conversions to open surgery were reported. At least 11 of these conversions were due to venous adhesions [5]. The conversion rate ranged from 0% to 55%, blood loss ranged from 200 to 842 mL, and operative time ranged from 397 to 518 min. A graft was used for venous reconstruction in 28 patients (20%). Eight deaths (5.7%) were reported postoperatively. Mortality ranged from 0% to 8% in the series, and reoperation was rarely described and reported in five patients (3.5%).

DISCUSSION

The wide application of MIS for almost every procedure in digestive surgery during the last twenty years has not involved pancreatic surgery. Reasons for this reluctance are related to the technical challenge of the dissection and reconstruction phases of PD. The fear of having bleeding difficult to control laparoscopically and the challenges posed by the pancreatoenteric reconstruction in the presence of a soft pancreas could have contributed to this phenomenon.

However, expert centres with a large volume of open pancreatic resections have introduced gradually MIS for PD over the last ten years. The increase in experience achieved with standard PDs performed robotically or laparoscopically has allowed these centres to adopt the MIS approach for extended pancreatectomy with vascular resection. The first series described was in 2011 by Giulianotti *et al.* [16], who reported two cases of lateral venous resection

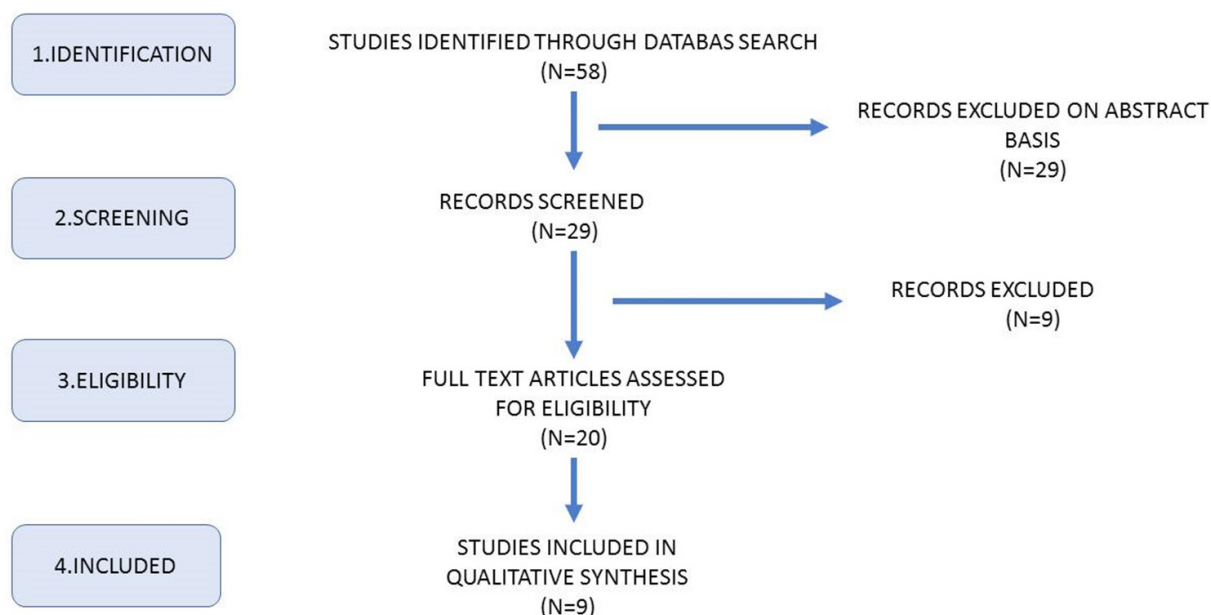


Figure 1. PRISMA flow chart of study selection

during robotic PD. Since then, further studies have reported experience with this approach. This current review found 140 PD with venous resection, of which 50% were performed robotically.

Most of these minimally invasive PDs with venous resection were lateral resections (58.5%), which needed either direct suture-repair or patch-interposition. This is certainly related to less advanced cases operated by MIS and to the challenges posed by segmental resection. Segmental resection is, in fact, needed more often in case of long and circumferential venous involvement; can require extensive mesenteric mobilization in order to achieve a tension-free venous approximation; and can require prolonged vascular clamping which can cause bowel oedema impairing the endoscopic view. The largest series to date of robotic PD with venous resection (50 cases) reported only one case of segmental resection^[12], whereas Croome *et al.*^[14] reported 9 over 22 cases of laparoscopic segmental venous resection.

Patch-repair was the technique of choice in case of a large defect of the lateral venous wall. Peritoneal, bovine pericardium and polytetrafluoroethylene material were variably used for venous patches. Postoperative thrombosis was rarely reported^[3,15,17]. We found a 5.7% postoperative mortality rate which is in the range of that reported in large registry studies in Europe^[20,21]. The causes of mortality were not different to those in open PD, with no specific complications related to the approach used. Blood loss and operative time seem to be comparable to that reported for open surgery.

In conclusion, despite limited experience, the minimally invasive approach to PD with venous resection seems feasible, with an acceptable rate of mortality and morbidity in the hands of highly experienced pancreatic surgeons. The advantages of this approach over open surgery remain to be determined.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Case Report

Open Access



Primary lung carcinoma with tracheal bronchus treated with uniportal video-assisted thoracoscopic upper lobectomy: a case report

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Abstract

Tracheal bronchus is a rare, congenital abnormality of the tracheobronchial tree. Majority of patients with tracheal bronchus are asymptomatic. Lung malignancy associated with tracheal bronchus is rare. An asymptomatic 40-year-old female was diagnosed with right upper lobe lung carcinoma. CT thorax revealed a right upper lobe tracheal bronchus. The patient underwent right uniportal video-assisted thoracoscopic (VATS) lobectomy and recovered well. To our knowledge, this is the first reported case of primary lung carcinoma with tracheal bronchus treated with right uniportal VATS upper lobectomy in Malaysia, and the second reported case internationally.

Keywords: Case report, tracheal bronchus, primary lung carcinoma, uniportal video-assisted thoracoscopic, lobectomy

INTRODUCTION

Bronchovascular variations exist in the general population but are often only diagnosed pre- or intra-operatively. Tracheal bronchus is a rare congenital variation of the bronchial tree structure and can be seen in 0.1%-3% of population^[1-5]. Primary lung cancer in association with tracheal bronchus is an even rarer entity^[1,6,7]. We present a case of a middle-aged female with right upper lobe carcinoma, tracheal bronchus and other bronchovascular variations, who underwent uniportal video-assisted thoracoscopic (VATS) right upper lobectomy and lymphadenectomy.



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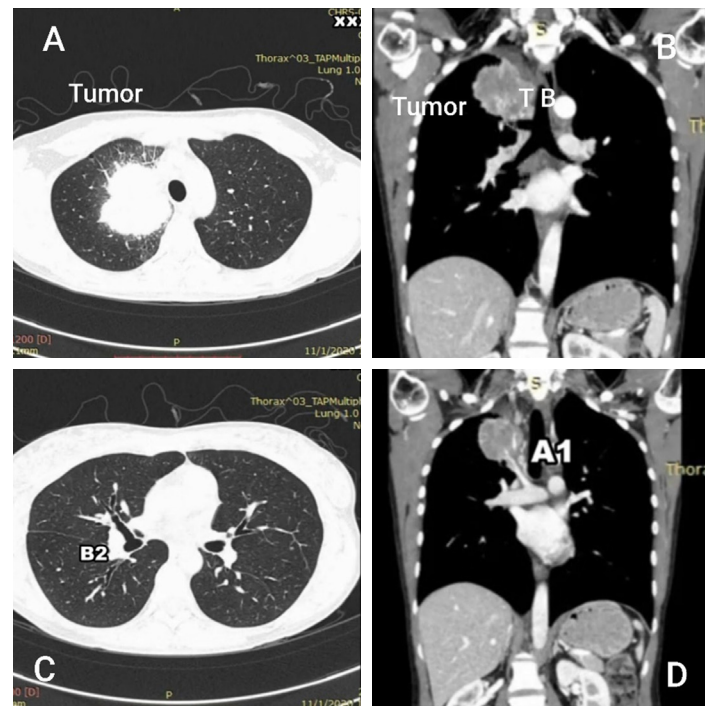


Figure 1. A: axial view of CT thorax showing a right upper lobe mass; B: coronal view of CT showing right upper lobe mass and tracheal bronchus; C: axial view of CT showing posterior segment bronchus (B2) originating from intermedius bronchus; D: coronal view of CT thorax showing artery to apical segment (A1) arising from the right main pulmonary artery. TB: tracheal bronchus

CASE REPORT

A 40-year-old female was referred to our Thoracic Surgery unit for right upper lobe carcinoma. She initially presented to a primary health care centre with digital clubbing, but no other respiratory symptoms. The patient was a chronic smoker, with a 20 pack year history.

Besides digital clubbing, the patient's physical examination was unremarkable. A chest radiograph revealed a large right upper lobe lesion. Subsequently, a CT thorax revealed a right upper lobe mass, measuring 5.6 cm × 5.1 cm × 5.7 cm [Figure 1A]. CT-guided biopsy of the lesion was performed, and histopathological examination determined the lesion to be an adenocarcinoma. PET CT demonstrated localized disease.

The patient's lung function test was acceptable, with a predicted postoperative forced expiratory volume in one second (PPOFEV1) of 81% for right upper lobectomy. Her CT was reviewed in the Thoracic Surgery outpatient clinic, and it was then noted that the patient had a right upper lobe bronchus originating from the trachea, a tracheal bronchus [Figure 1B].

The patient underwent uniportal VATS right upper lobectomy and lymphadenectomy. Intraoperatively, the tumor measured 6 cm × 7 cm [Figure 2] and both the oblique and horizontal fissures were completely fused. Besides the tracheal bronchus, other anatomical variations were found. The posterior segmental bronchus (B2) was noted to be originating from the bronchus intermedius [Figures 1C and 3C], and the A1 artery was seen to be originating from the right main pulmonary artery [Figures 1D and 3D], while the A2 and A3 were from the truncus anterior [Figure 3D]. Lymph nodes at stations 2R, 4R, 7, 8 and 10 were dissected and cleared.

Surgery was performed entirely via uniportal VATS, with blood loss of approximately 100 mL. The patient's post-operative recovery was uneventful, and she was discharged home well on post-operative day 5. The



Figure 2. Resected right upper lobe with tumor

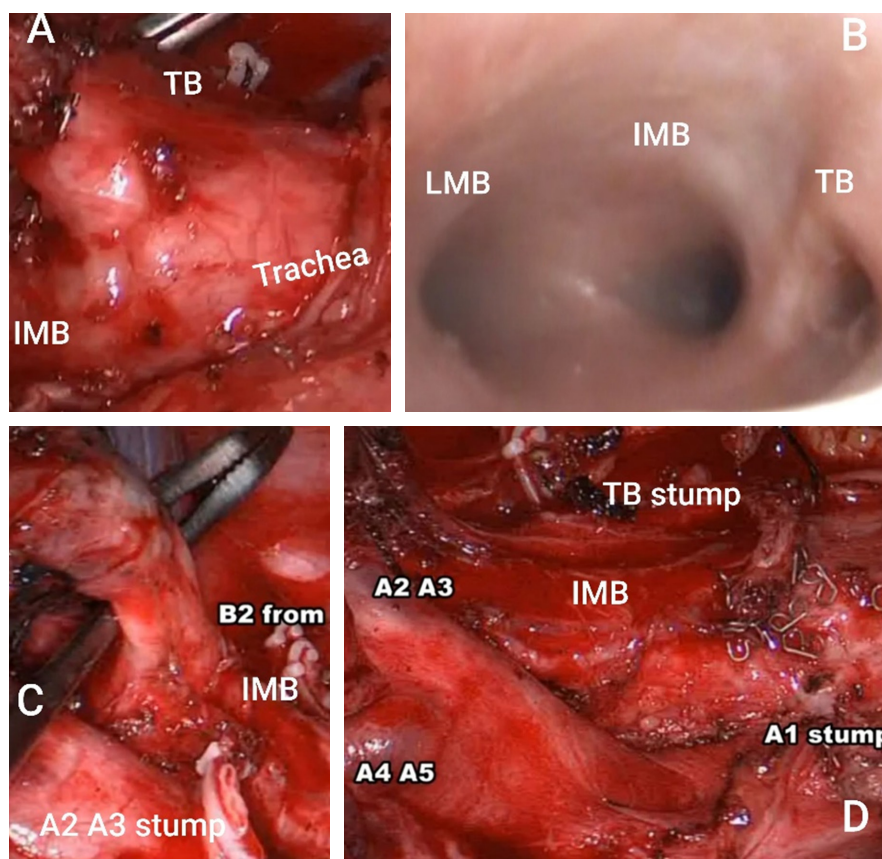


Figure 3. A: shows the TB arising from the trachea; B: an intraoperative bronchoscopy image which shows a right tracheal bronchus; C: shows the posterior segment bronchus (B2) arising from the intermedius bronchus; D: shows the arterial and bronchial supply post-resection. TB: tracheal bronchus; IMB: intermedius bronchus; LMB: left main bronchus

histopathological diagnosis was solid type adenocarcinoma, T3NO_(0/21) MO based on TNM staging, which translates to Stage IIB disease. The patient was later referred to an oncologist for adjuvant therapy. The surgical video is available for viewing at <https://youtu.be/93xKNmBR4Ns>.

DISCUSSION

Tracheal bronchus was first described by Sandifort in 1758^[1-3]. This condition is also known as bronchial suis or pig bronchus. It is a rare congenital anomaly, described as an ectolupic bronchus arising from the lateral wall of the trachea, proximal to the carina. The incidence of tracheal bronchus is reported to be between 0.1%-3%^[1-5].

Tracheal bronchus more commonly occurs on the right side (0.1%-3%) than the left (0.3%-1%)^[3,8]. Tracheal bronchus can arise anywhere between the carina and the cricoid cartilage, most commonly 2 cm from the carina. The highest origin of tracheal bronchus reported was 6 cm from the carina^[9]. Tracheal bronchus is also associated with other congenital abnormalities like Down's syndrome, tracheoesophageal fistula, VATER (vertebra, anus, trachea, esophagus, renal) syndrome, esophageal atresia, laryngeal and duodenal webs, spinal fusion defects and congenital cardiac defects^[3,4,8,9]. Amongst patients with tracheal bronchus, 69% have associated cardiac disease, 35% have associated chromosomal abnormalities and 11% have spinal fusion defects.

Generally, tracheal bronchus can be classified into displaced and supernumerary types. In the displaced type, there is a missing segmental bronchus from the right upper lobe bronchus. In the supernumerary type, the right upper lobe bronchus trifurcates into apical, posterior and anterior segmental bronchi^[7,9,10]. The patient in this case report had a displaced tracheal bronchus, as the posterior segmental bronchus originated from the intermedius bronchus.

Another categorization of tracheal bronchus considers the distance of the tracheal bronchus origin from the carina. According to this classification, tracheal bronchus is divided into 3 types: (1) Type I: tracheal bronchus originates more than 2 cm from the carina, with narrowing of the distal trachea; (2) Type II: tracheal bronchus originates more than 2 cm from the carina, no narrowing of the distal trachea; (3) Type III: tracheal bronchus originates less than 2 cm above the carina.

Majority of patients with tracheal bronchus are asymptomatic. Symptomatic patients usually present with recurrent chest infections due to retained secretions. Symptomatic children usually present with stridor and recurrent pneumonia^[1,2,6,8,10]. Treatment is advocated for patients with severe, recurrent symptoms, with definite treatment being an upper lobectomy. Asymptomatic patients do not require intervention. Despite being asymptomatic, our patient required intervention due to the incidental mass found on chest X-ray.

Presence of a tracheal bronchus may present a challenge for anesthetists as problems can arise during intubation. The anomalous bronchus may get occluded by the endotracheal tube, resulting in right upper lobe collapse and shunting. Accidental intubation of the anomalous bronchus can also lead to pneumothorax^[5,7,10].

Malignancy arising from a tracheal bronchus is rare. Besides malignancy, there have also been case reports on tuberculosis, leiomyoma and massive hemoptysis associated with tracheal bronchus^[7]. To date, less than 20 cases of primary lung malignancy associated with tracheal bronchus have been reported. Uchikov *et al.*^[11] in Bulgaria was the first to report a case of lung malignancy arising from tracheal bronchus in 1974. The second case report in the world was published in 1985 by Moriya *et al.*^[12], regarding a Japanese patient with small cell lung cancer which was seen originating from a tracheal bronchus. Due to the rarity of this pathology, no studies have been performed to investigate the association between a tracheal bronchus and

primary lung malignancy^[6]. Yurugi *et al.*^[2] were the first to report a case of VATS right upper lobectomy for lung cancer with tracheal bronchus, utilizing a 5-port technique. Huang *et al.*^[1] were the first to report a case of uniportal right VATS upper lobectomy for lung cancer associated with tracheal bronchus. To date, this is the first case report from Malaysia, and to the authors' best knowledge, the second case report internationally, of a patient with primary lung carcinoma, with a tracheal bronchus, to have undergone right upper lobectomy via uniportal VATS.

Variations in bronchovascular patterns are common, hence it is important for a thoracic surgeon to look out for these variations, both pre- and intra-operatively, in order to prevent devastating outcomes. In a study by Nagashima *et al.*^[13], bronchovascular patterns of the right upper lobes of 263 patients were reviewed using 3D CT angiography and bronchography images. Based on their study, 71.9% (189 patients) had the usual pulmonary artery branching, and 44.1% (116 patients) had the usual upper lobe bronchial branching, as classically described in most textbooks^[13]. The remaining patients had variations in bronchovascular supply to the right upper lobe. In 13.3% of patients, the origin of A1 and A3 varied, as in the subject of this case report.

In conclusion, primary lung carcinoma with associated tracheal brochus is rare. A myriad of other bronchovascular variations exists, with or without an associated tracheal bronchus. It is imperative for thoracic surgeons to have thorough knowledge on bronchovascular pattern variations, and to perform thorough dissection during surgery in order to avoid devastating outcomes. In the hands of an experienced surgeon, with detailed preoperative planning, uniportal VATS lobectomy can be safely performed with good outcomes and low morbidity.

DECLARATIONS

Authors' contributions

Collected and selected articles: Dharmaraj B

Participated in manuscript, writing and review: Dharmaraj B, Sathiamurthy N, Diong NC, Balasubbiah N

Participated in review: Dharmaraj B, Sathiamurthy N

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Approval obtained from the office of the Director and the hospitals' ethics committee to proceed with this analysis and publication.

Consent for publication

The author(s) declared that informed consent has been taken from the patient for usage of peri-operative data and images for publication purpose.

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Review

Open Access



The technique of robotic anatomic pulmonary segmentectomy I: right sided segments

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Abstract

Anatomic pulmonary segmentectomy and mediastinal nodal dissection have been advocated in patients with smaller tumors or patients with limited pulmonary reserve. The overall five-year survival and lung cancer-specific five-year survival following anatomic segmentectomy have been shown to be equivalent to lobectomy. Robotic surgical systems have the advantage of magnified high-definition three-dimensional visualization and greater instrument maneuverability in a minimally invasive platform. Robotics can facilitate the dissection of the broncho-vascular structures and replicate the technique of segmentectomy by thoracotomy. Greater experience with the robotic platform has resulted in a reproducible technique. The Technique of Robotic Anatomic Segmentectomy Part I outlines a stepwise approach to robotic segmentectomy of S1, S2, S3, S4, S5, S6, and S7-S10 of the right lung. The Technique of Robotic Anatomic Segmentectomy Part II outlines a stepwise approach to robotic segmentectomy to the left lung.

Keywords: Robotic, segmentectomy, lung cancer, superior segment, anterior segment, apicoposterior segment, basal segment, sublobar resection

INTRODUCTION

Anatomic segmental resection (segmentectomy) is the excision of one or more bronchopulmonary segments of a pulmonary lobe with individual ligation and division of the corresponding broncho-vascular



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structures. It is important to differentiate segmentectomy from “wedge resection”, which is a form of sublobar resection. A wedge resection is defined as removal of a portion of the lung along non-anatomic planes usually with the aid of a stapling device.

Controversy about sublobar lung resection is largely attributed to The Lung Cancer Study Group’s prospectively randomized study in 1995 which showed that sublobar resections (a combined cohort of anatomic segmentectomies and wedge resections) had 75% increased recurrence, 30% increased overall death, and 50% increased cancer-related death compared to lobectomy^[1,2]. This study did not differentiate between anatomic segmentectomy and wedge resection. Subsequently, multiple retrospective studies have shown that in general segmentectomies have lower recurrence rates and better survival than wedge resections^[3-7]. On the other hand, in a retrospective study of patients with T1N0 disease, Altorki *et al.*^[8] showed that anatomic segmentectomy and wedge resection are comparable oncologic procedures. In addition, although anatomic segmentectomy was associated with a more thorough lymph node dissection, it did not offer a survival advantage in this group of patients with early disease. Although prospective studies comparing wedge resection and anatomic segmentectomy for T1N0 disease are in progress, anatomic segmentectomy may be a better oncologic procedure in patients with more advanced disease. Furthermore, multiple retrospective studies have demonstrated no significant difference in oncologic outcomes with anatomic segmentectomy versus lobectomy^[9-12].

As the result of these findings, recently, there has been renewed interest in segmentectomy for small primary lung cancer tumors, as well as in patients with marginal pulmonary reserve^[13].

Robotic surgical systems have the advantage of high definition three-dimensional visualization, precise instrument maneuverability in a confined space, and decreased surgeon fatigue. The surgical robot is ideally suited for performing minimally invasive anatomic segmentectomy. It allows for precise dissection of the segmental bronchopulmonary structures while minimizing trauma to surrounding tissue and allows for thorough complete dissection of the mediastinal nodes. Dylewski reported the first experience with robotic anatomic segmentectomy^[14]. In this study, robotic segmentectomy had a lower complication rate than robotic lobectomy (11.4% vs. 31%). Pardolesi and Cerfolio reported a similar experience^[15-17]. Demir reported that VATS and robotic segmentectomy have similar morbidity and mortality^[18]. Nguyen *et al.*^[19] used the Standard da Vinci and Si da Vinci platforms and replicated the anatomic segmentectomy technique as performed by a thoracotomy. In their experience, the robotic approach was used for the apical, anterior, and posterior segments of the upper lobe; the superior segment of the lower lobe on the right; the apical, anterior, and posterior segments of the upper lobe; and the lingual and superior segment of the lower lobe on the left.

This paper outlines a step by step approach to robotic anatomic segmentectomy to the segments of the right lung. The segmental anatomy of the right lung is illustrated in [Figure 1](#).

RIGHT SIDED SEGMENTECTOMY

Port placement

Port placement for anatomic segmentectomy is the same as with pulmonary lobectomy.

The operating room table is reversed such that the pedestal does not interfere with the docking of the robot over the head of the patient.

A double lumen endotracheal tube is placed, and the patient is positioned in a full lateral decubitus position. The double lumen endotracheal tube is preferable to a bronchial blocker. The manipulation of the lung and the hilum can dislodge the bronchial blocker and result in loss of exposure during robotic

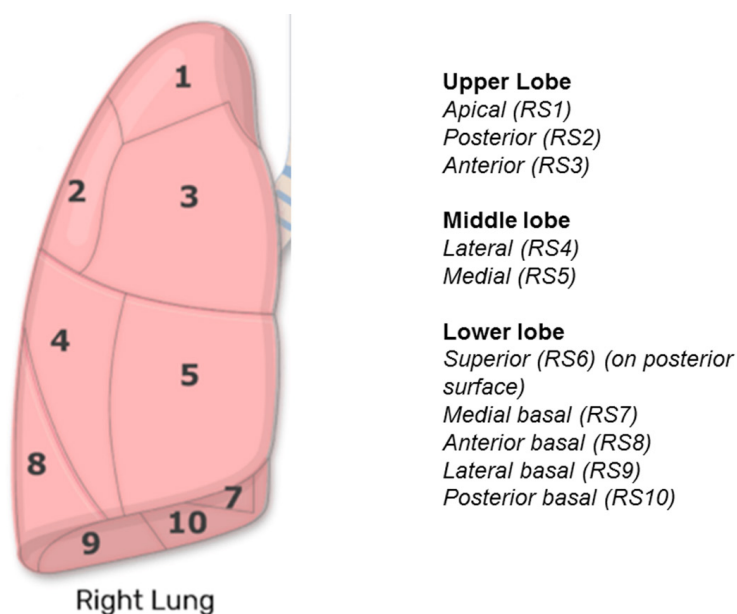


Figure 1. Right lung bronchopulmonary segments

lung surgery. In addition, as the robot is positioned over the head of the patient, with the robot in place, manipulation and replacement of the endobronchial blocker is very cumbersome. The right arm is placed over pillows and positioned high enough such that access to the 4th intercostal space in the anterior axillary line is readily attained. The table is flexed to move the hip down and to open the intercostal spaces. The lung is deflated and placed on suction. The position of the double lumen tube is rechecked after the patient is prepped and draped. It is imperative that the lung remain isolated throughout the procedure.

Figures 2 and 3 show the right chest port placement. A line is drawn from the tip of the scapula to the costal arch. This delineates the highest point in the chest and the midscapular line (corresponding to the posterior axillary line with the arm at the side of the patient). Pleural entry is with a Hassan needle. Saline is infused and care is taken to look for easy egress of the saline from the needle. If there is any question of pleural adhesions, the Visiport Instrument (Medtronic Inc. Norwalk, Conn, USA) is used for entry into the pleural space under direct vision. If the Visiport is used, a purse string is placed in the muscle layer and tied around the robot camera port to prevent CO₂ leakage.

Port #1 is the camera port. Warm, humidified CO₂ is insufflated through this port at a flow of 6 L/min to a pressure of 6-8 mmHg in order to push the lung and diaphragm away. The other ports are placed under direct vision. Port #2 (8 mm) is placed in the 7th intercostal space in the poster scapular line. This port is 9 cm posterior to Port #1 and accommodates da Vinci arm #2. Prior to the placement of Port #3, a 21-gauge needle is inserted into the 7th intercostal space at costovertebral junction from the patient's back and injects a 10-mL subpleural bubble of 0.25% bupivacaine with epinephrine near the intercostal nerve. Next, Port #3 is placed 10 cm posterior to Port #2 in the 7th intercostal space just medial to the spine. This port accommodates da Vinci arm #3. Port #4 is placed 9 cm anterior to Port #1 in the 7th intercostal space at the anterior scapular line. This port accommodates da Vinci arm #1. The Assistant Port #5 uses a 10-12 Versiport (Medtronic Inc. Norwalk, Conn, USA) trocar, is placed in the 9th intercostal space, and is triangulated between Ports #1 and #4. It should be two or three ribs lower than the da Vinci ports and as far away as possible to maximize assistant workspace. Keeping this port off the trajectory lines for the other ports will facilitate the patient-side assistant's access for retraction and other maneuvers. In total, including the vitally important assistant port, robotic anatomic segmentectomy is performed with five ports. The use of

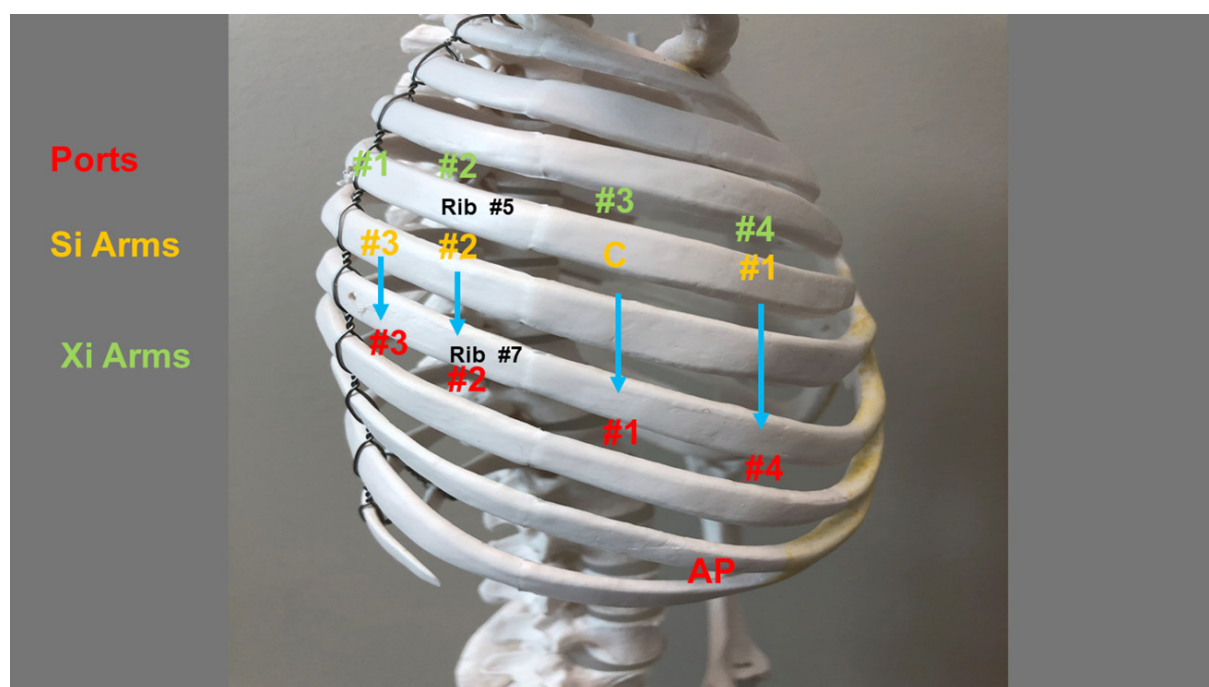


Figure 2. Schematic of port placement for robotic segmentectomy in the right chest. Ports are in red, Si arms are in yellow, and Xi arms are in green. AP: assistant port

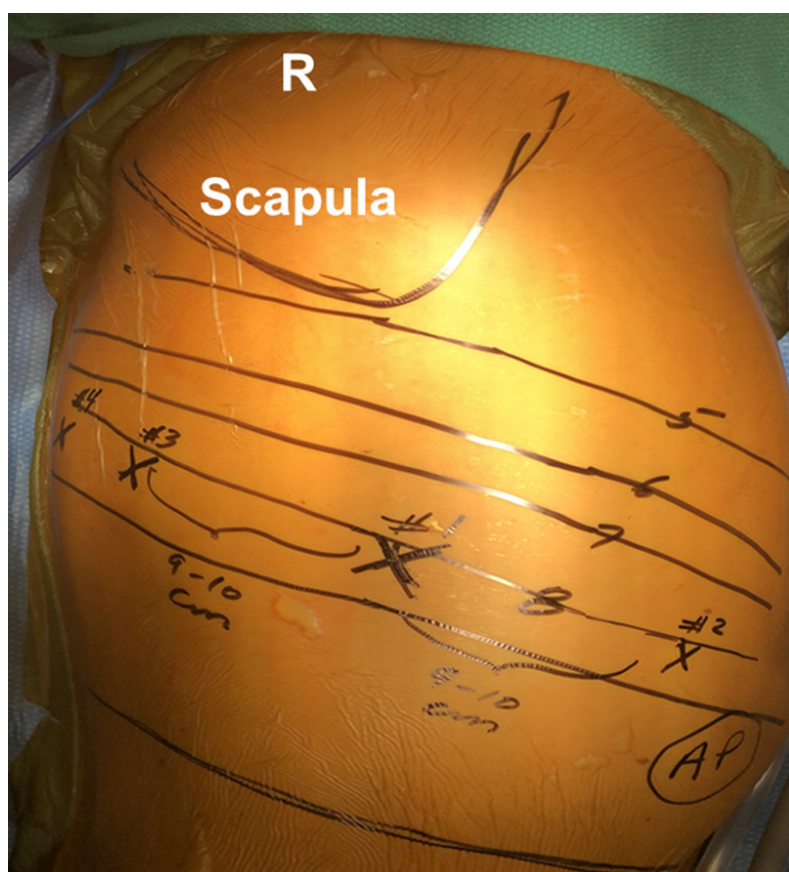


Figure 3. Port placement for robotic segmentectomy in the right chest. Patient is in full lateral decubitus position. Robot arms are numbered #1, #2, #3, and #4. AP: assistant port

additional ports should be tailored to the specific situation and the experience of the surgeon. Surgeons are encouraged to use as many ports as are necessary to perform a safe and oncologically efficacious anatomic segmentectomy.

Port placement and intercostal sites are the same for all segments. All effort should be made to keep the distance between the ports as close as possible as to what is described above. In smaller patients, care must be taken to keep the trocar sites as far as possible and within the parameters that are outlined. This strategy prevents interference in arm function with the present robotic platforms. It is possible that port placement may be modified in the future with the development of new platforms and robot arms which may have a smaller “footprint” on the chest.

Port Placement with Si Robot: Robotic arm #3 is located two cm lateral from the spinous process of the vertebral body, robotic arm #2 is 10 cm medial to robotic arm #3, the camera port (we prefer the 12-mm camera) is 9 cm medial to robotic arm #2, and robotic arm #1 is placed right above the diaphragm anteriorly.

Port Placement with Xi Robot: For the Xi system, the ports are placed in slightly different locations. They are also numbered differently. Robotic arm #1 is placed 4 cm away from the spinous process. Robotic arm #2 is placed 8 cm from arm #1 and robotic arm #3 is placed 8 cm from arm #2. Robotic arm #4 is placed right above the diaphragm anteriorly. The assistant port is triangulated behind the camera arm and robotic arm #4 in a similar fashion. The camera is carried by arm #3. Arms #1-#4 are all placed in the 7th intercostal space. The Xi robot has the advantage of providing the robotic stapler, which gives the surgeon control of the stapling and the use of indocyanine green dye for identification of the intersegmental plane.

Instruments: 0° and/or 30° down viewing endoscope, 5 mm Thoracic Grasper (left ③), Cadiere Forceps (left ②), and Curved Bipolar Dissector (right ①).

Mediastinal nodal dissection

Complete nodal dissection is performed with all anatomic segmentectomy procedures. Begin by dividing the inferior pulmonary ligament and remove Station #9 and #8 nodes [Figure 4]. The most posterior arm is used to retract the lower lobe medially and anteriorly to remove lymph nodes from Station #7. Next, open the pleura anterior to the vagus nerve and divide the anterior branch of the nerve which traverses the subcarinal space. At the beginning of the case, a nasogastric tube should be inserted to decompress the stomach. After decompression of the stomach, some surgeons may prefer to remove the nasogastric tube to aid in the retraction of the esophagus during the subcarinal dissection. This opens the subcarinal space and allows for better access to the Station #7 nodes. Identify the right mainstem bronchus and stay posterior to the edge of the cartilage. Remove the Station #7 nodes and control the subcarinal artery at the carina. At the end of the dissection, the right and left mainstem bronchi should be visible and the posterior aspect of the pericardium should be cleaned and clearly visible [Figure 5]. Next, the most posterior arm is used to retract the upper lobe inferiorly during dissection of Stations #2R and #4R, clearing the space between the superior vena cava anteriorly, the trachea posteriorly, and the azygos vein inferiorly [Figure 6].

Completion of the lymph node dissection opens the mediastinal space and facilitates the dissection of the artery and the bronchus. After identifying the right mainstem bronchus, it is followed up to the level of Station #10R lymph node [Figure 7]. This node is superior to the right mainstem bronchus. It should be dissected and swept towards the lung, thereby exposing the bronchus and the truncus branch of the pulmonary artery.

Dissection is continued and the crotch between the right upper lobe bronchus and bronchus intermedius is defined. All Station #7 and #11 nodes and the sump node are removed. This maneuver facilitates later

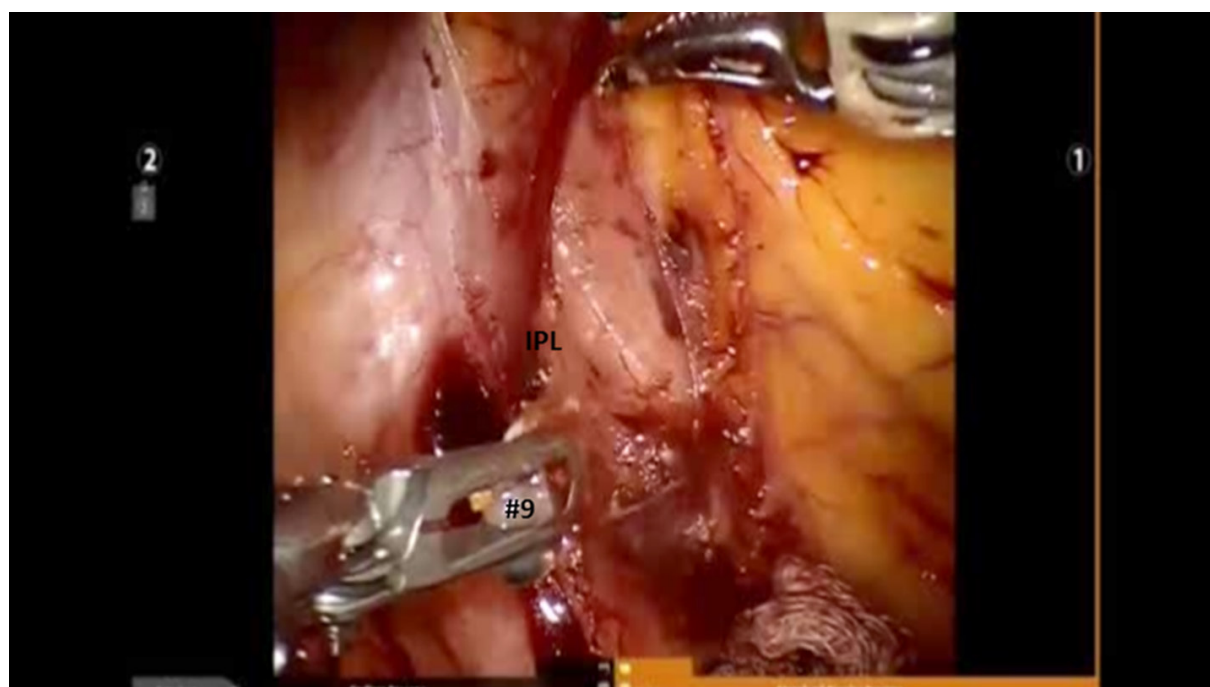


Figure 4. The IPL is divided and Station # 9 nodes are removed. IPL: inferior pulmonary ligament

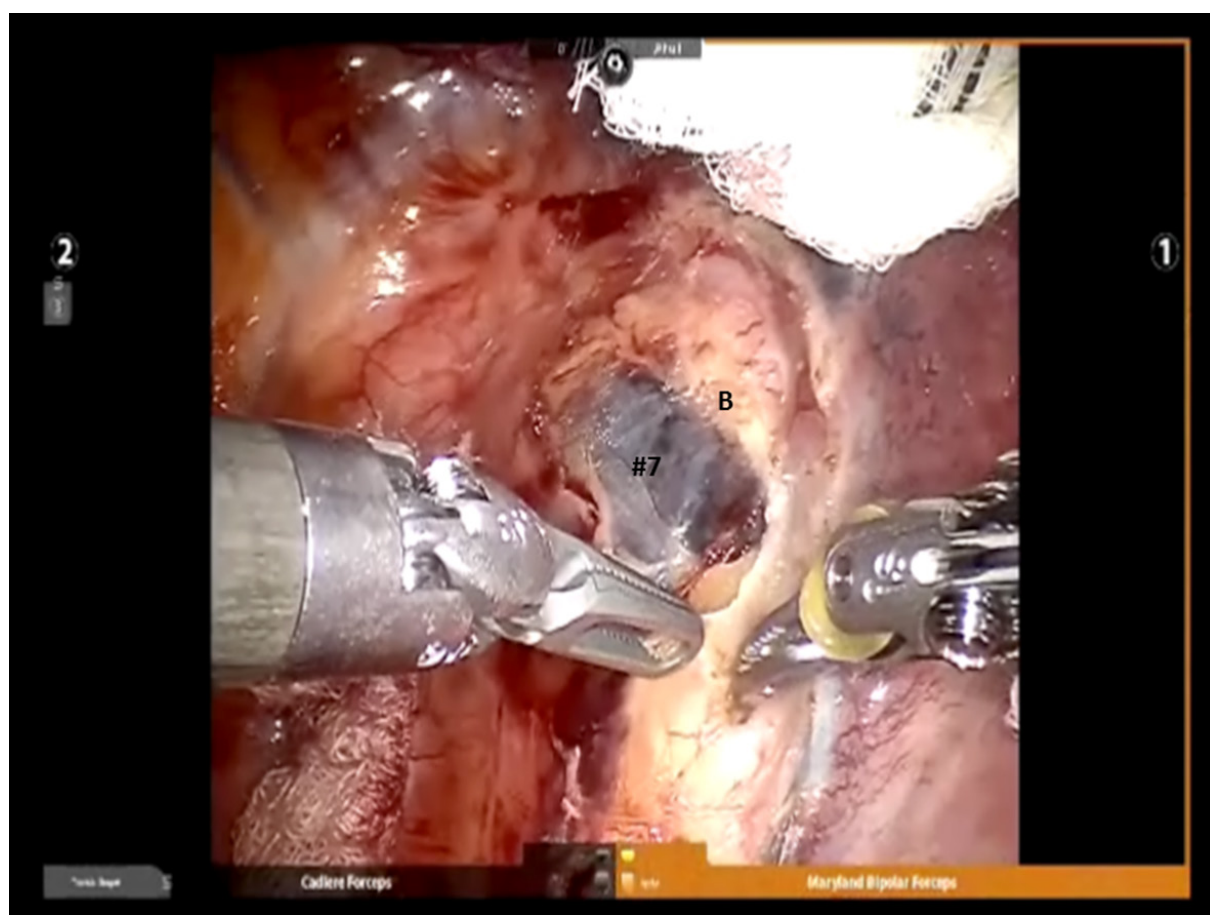


Figure 5. Subcarinal dissection: View of the right mainstem bronchus (B) and Station #7 lymph nodes

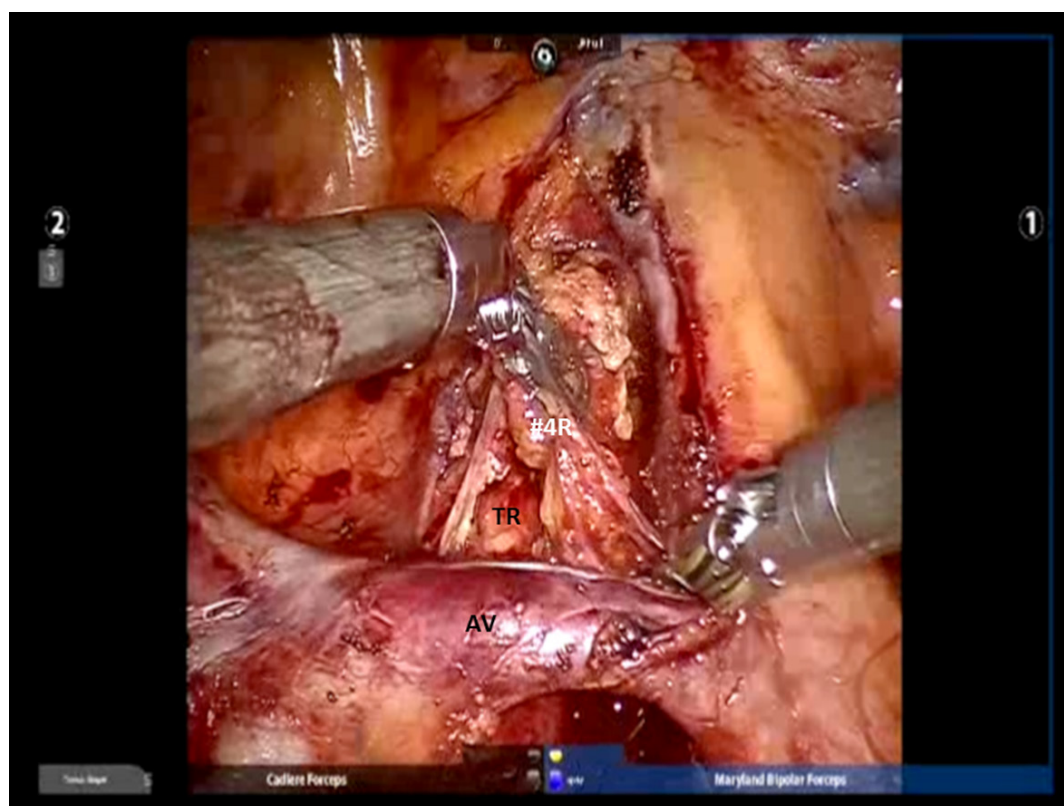


Figure 6. Dissection of the right paratracheal space: View of the #4R nodal bundle, AV, and TR. AV: azygous vein; TR: trachea

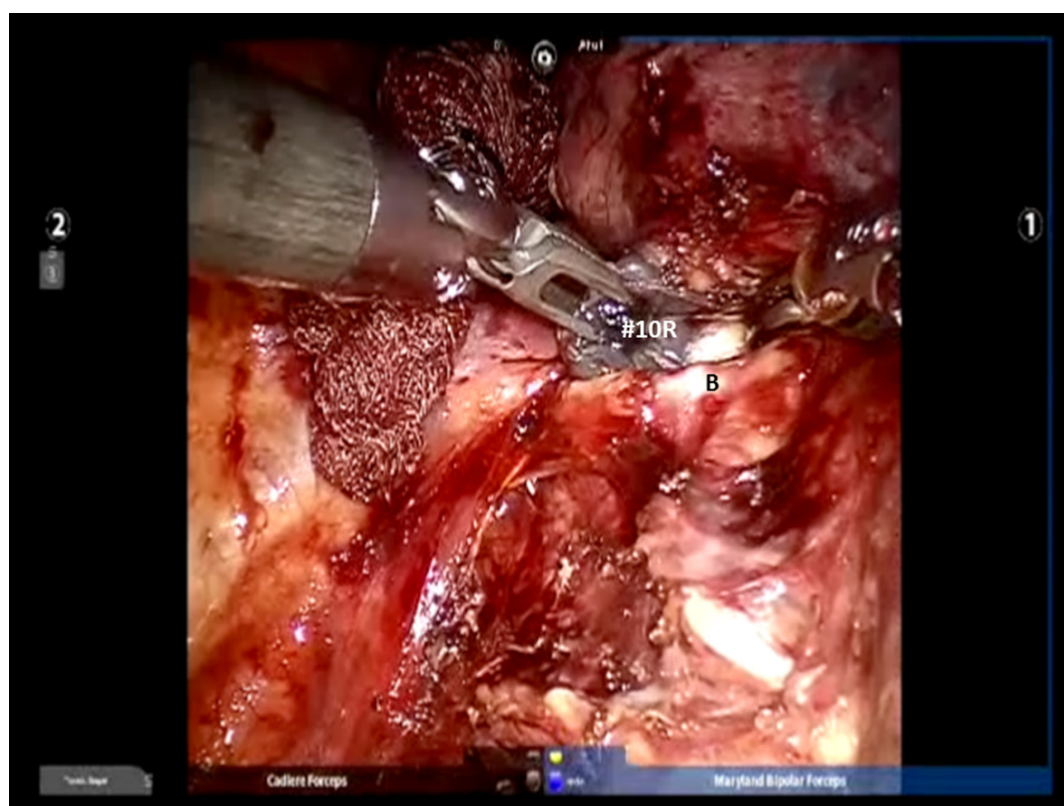


Figure 7. Dissection of #10R Nodal bundle: The nodes are above the right mainstem bronchus (B). Removal of the nodes facilitates getting around the bronchus

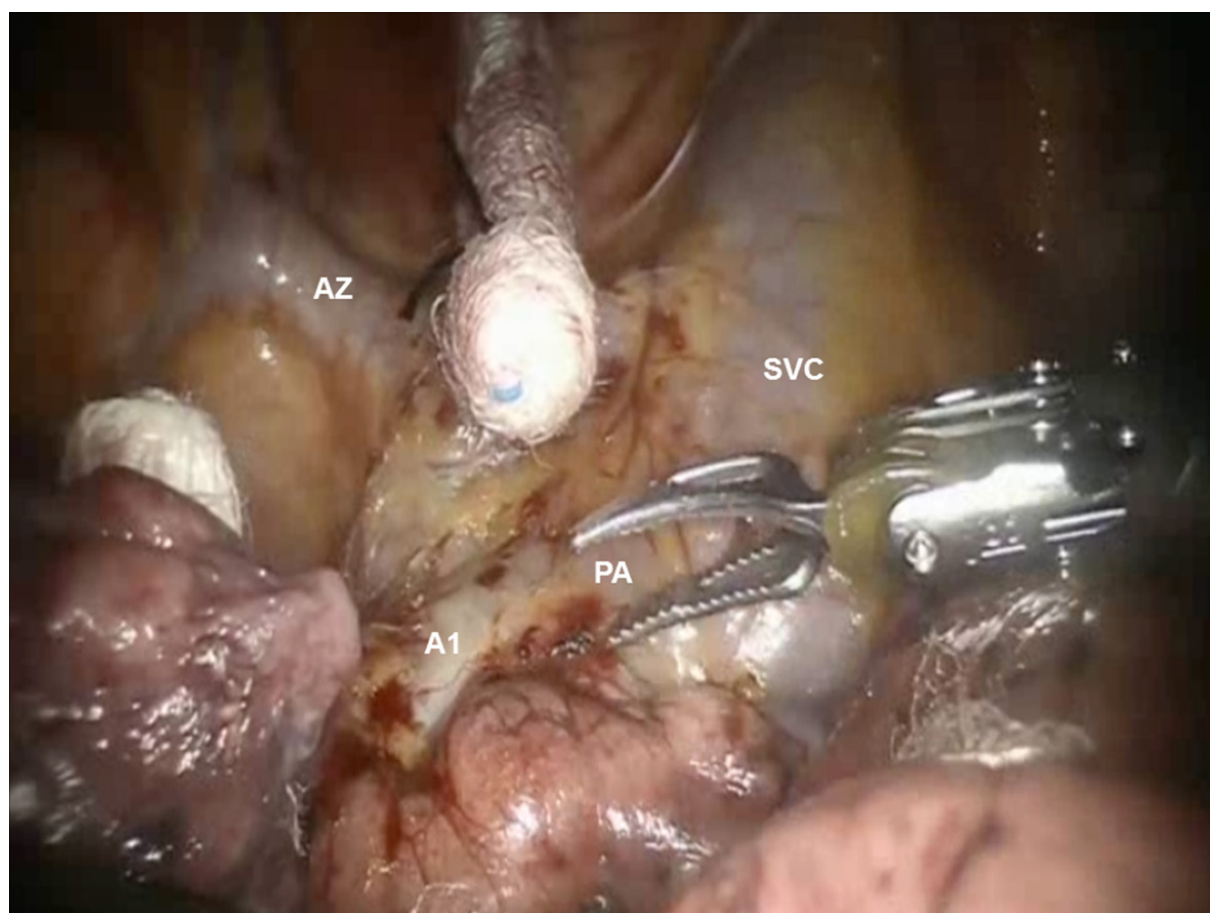


Figure 8. R51 segmentectomy: Dissection of the A1 branch of the PA. View of the SVC, AZ, and the right main PA. AZ: azygous vein; PA: pulmonary artery; SVC: superior vena cava

dissection of the pulmonary artery (PA) as well as the right upper lobe bronchus. In addition, the removal of Station #11 nodes facilitates the completion of the posterior fissure.

Next, the lung is retracted posteriorly to expose the anterior hilum. The dissection is carried down between the hilar structures and the phrenic nerve. The phrenic nerve is swept down to remove the #10R lymph node. The bifurcation between the middle and upper lobe veins is dissected. It is best to encircle the entire upper lobe vein off the underlying PA using the Cadere Forceps in the left arm and pass a red rubber vessel loop to elevate the vein. This makes the dissection of the middle lobe vein easier. Following the dissection of the middle lobe vein, the Cadere Forceps is passed under the elevated upper lobe vein, and the vessel loop is released and regrasped, thereby isolating the upper lobe vein. Dissection is continued and the proximal main PA is exposed as it emerges from the pericardium.

Right upper lobe anatomic apical segmentectomy (S1)

Following the complete mediastinal nodal dissection, the lung is retracted in a caudal direction and the A1 PA branch is identified, dissected away from the descending branch of the right PA, and divided using a stapler with a vascular cartridge [Figures 8 and 9]. Next, the lung is retracted posteriorly and the V1 branch of the superior pulmonary vein is identified [Figure 9]. The N1 nodal bundle which resides between the V1 and the PA is removed. V1 is encircled and divided with a stapler with a vascular cartridge. Although many surgeons do not anatomically isolate and divide the segmental vein separately, isolation and division of the vein helps in opening the operative space and may be preferred. Division of the vessels and removal of the

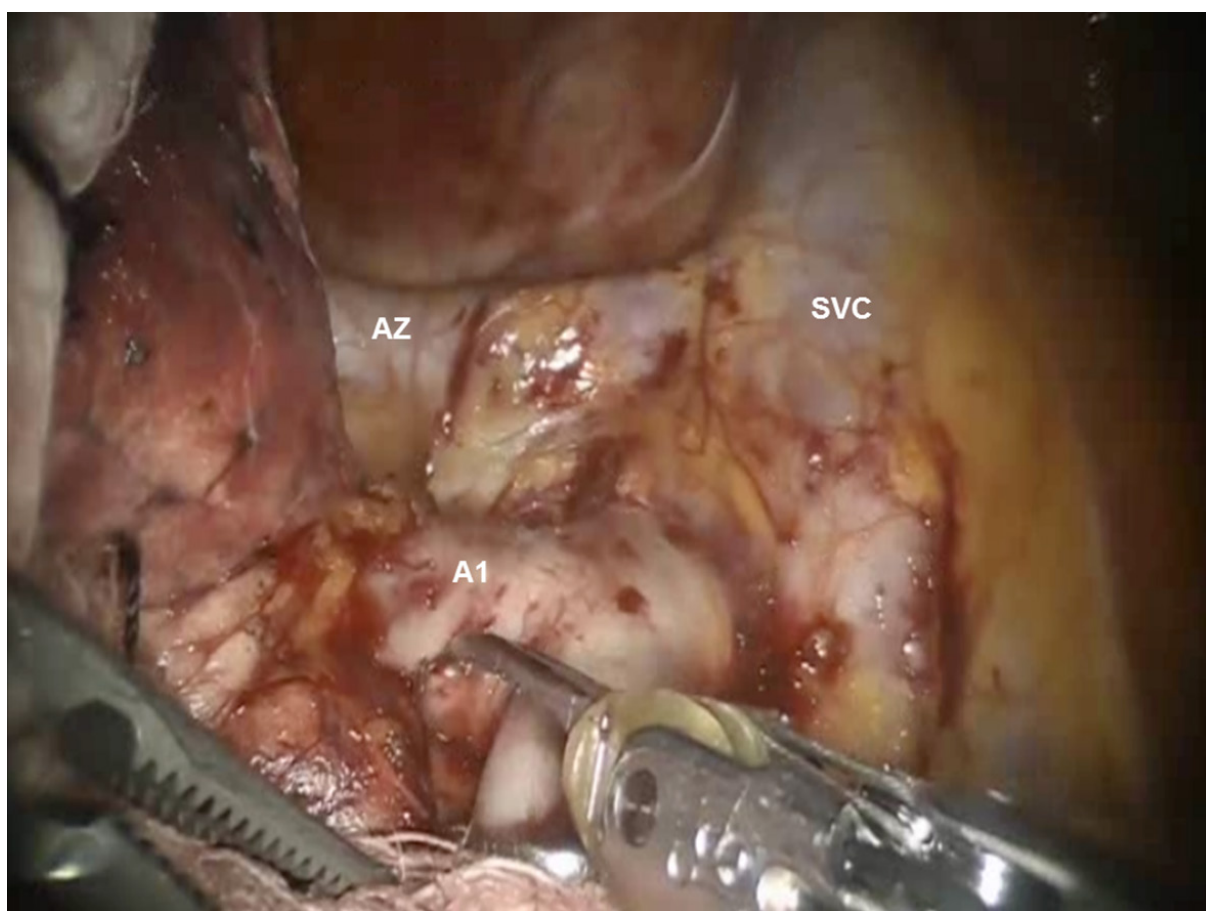


Figure 9. RS1 segmentectomy: Dissection of the A1 branch of the pulmonary artery. View of the SVC, AZ, and the right main pulmonary artery. AZ: azygous vein; SVC: superior vena cava

N1 nodes between the PA and the bronchus exposes the B1 bronchus. The B1 bronchus is encircled and divided with a stapler using a purple cartridge [Figure 10]. Prior to firing the stapler, the anesthesiologist must make certain that the suction catheter in the endotracheal tube is removed. Following the division of the B1 bronchus, if using the Xi robot, indocyanine green is injected and the fissure between the S1 and S3 segments is clearly delineated [Figure 11]. If using the Si robot, the anesthesiologist is instructed to gently inflate the lung to delineate the intersegmental fissure between S1 and S3. The intersegmental fissure is divided using a stapling device.

For all anatomic segmentectomies, the specimen retrieval bag (Anchor bag) is introduced through the accessory port; the specimen is placed into the bag; and the bag is removed.

Right upper lobe anatomic posterior segmentectomy (S2)

Following the complete mediastinal nodal dissection, the PA is identified in the oblique fissure [Figure 12]. Dissection is carried over the descending branch of the PA under the posterior aspect of the oblique fissure and cephalad to the superior segmental PA. The posterior oblique fissure is encircled with a vessel loop, retracted away from the PA, and divided with a stapling device. The upper lobe is retracted antero-medially, and dissection is carried cephalad on the PA until the truncus branches are identified. The V2 vein runs posteriorly from the superior pulmonary vein in the oblique fissure [Figure 13]. The V2 vein is dissected, encircled, and divided. Division of the V2 vein uncovers the A2 PA branch [Figure 14]. This is encircled with a vessel loop and divided using a stapler with a vascular cartridge. Next, the B2 bronchus is identified,



Figure 10. RS1 segmentectomy: The lung is retracted posteriorly and the V1 branch of the superior pulmonary vein is identified. View of the V1 pulmonary vein branch and SPV. LN: lymph node; SPV: superior pulmonary vein

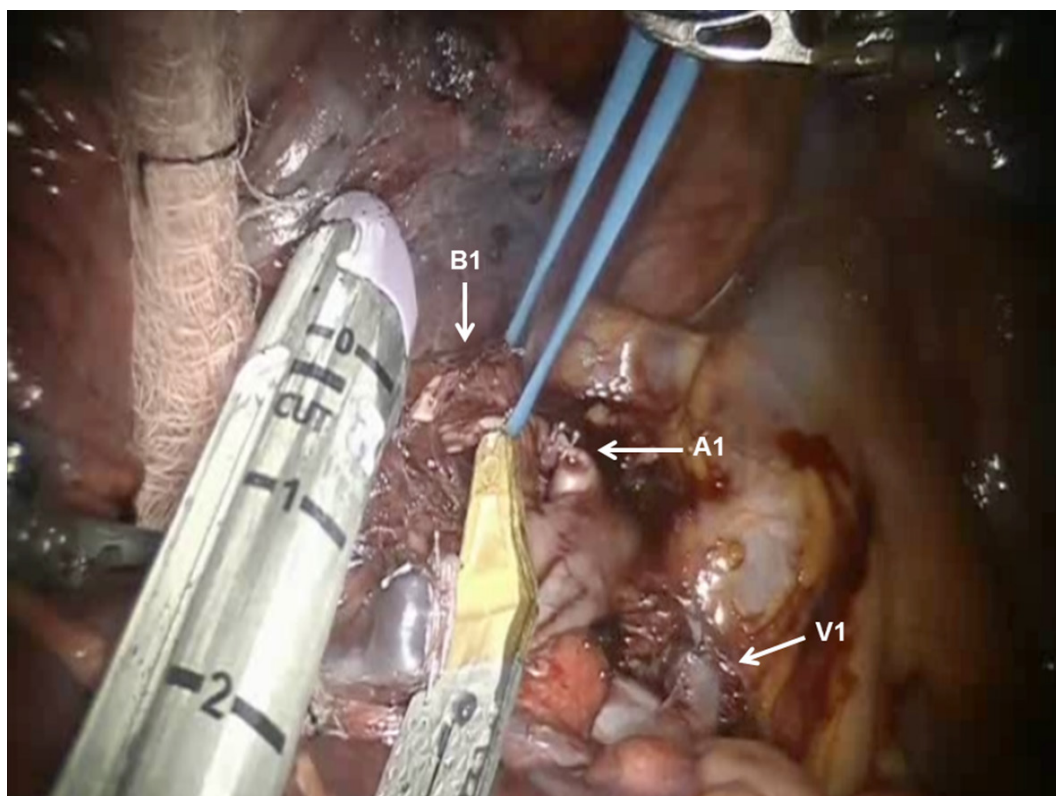


Figure 11. RS1 segmentectomy: B1 bronchus is encircled and divided with a stapler using a purple cartridge. Stapled stumps of the A1 Pulmonary artery and V1 Pulmonary vein branch are seen

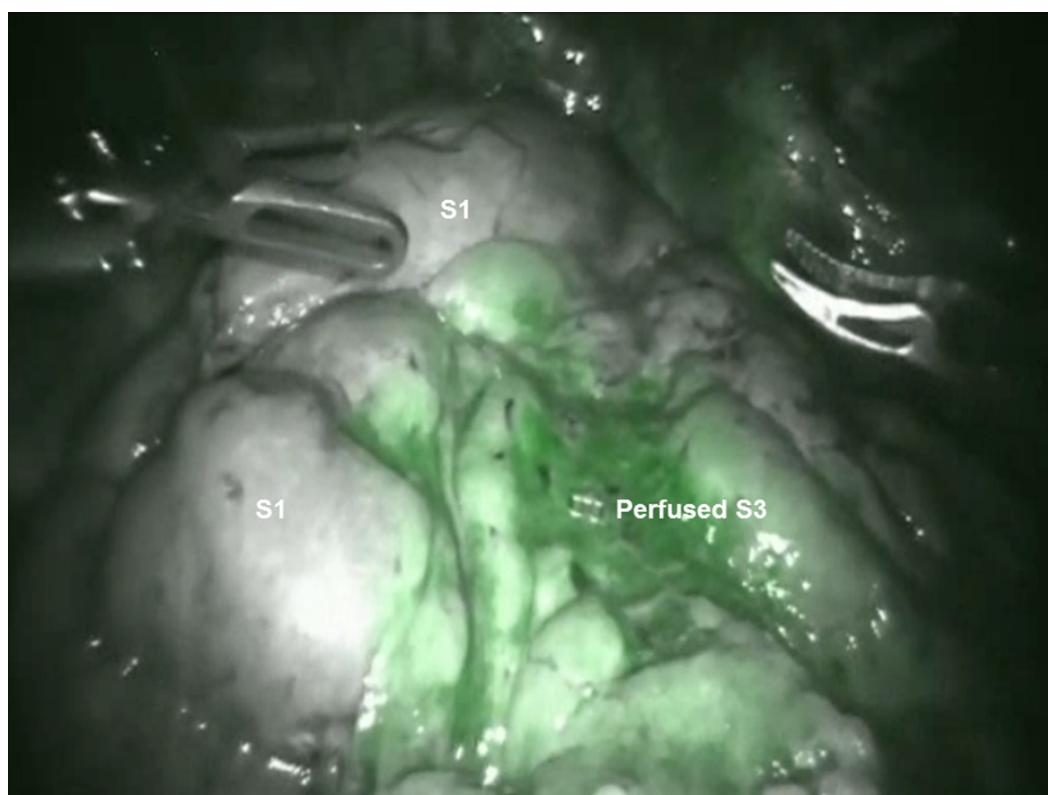


Figure 12. RS1 segmentectomy: Indocyanine green is injected and the fissure between the S1 and S3 segments is clearly delineated

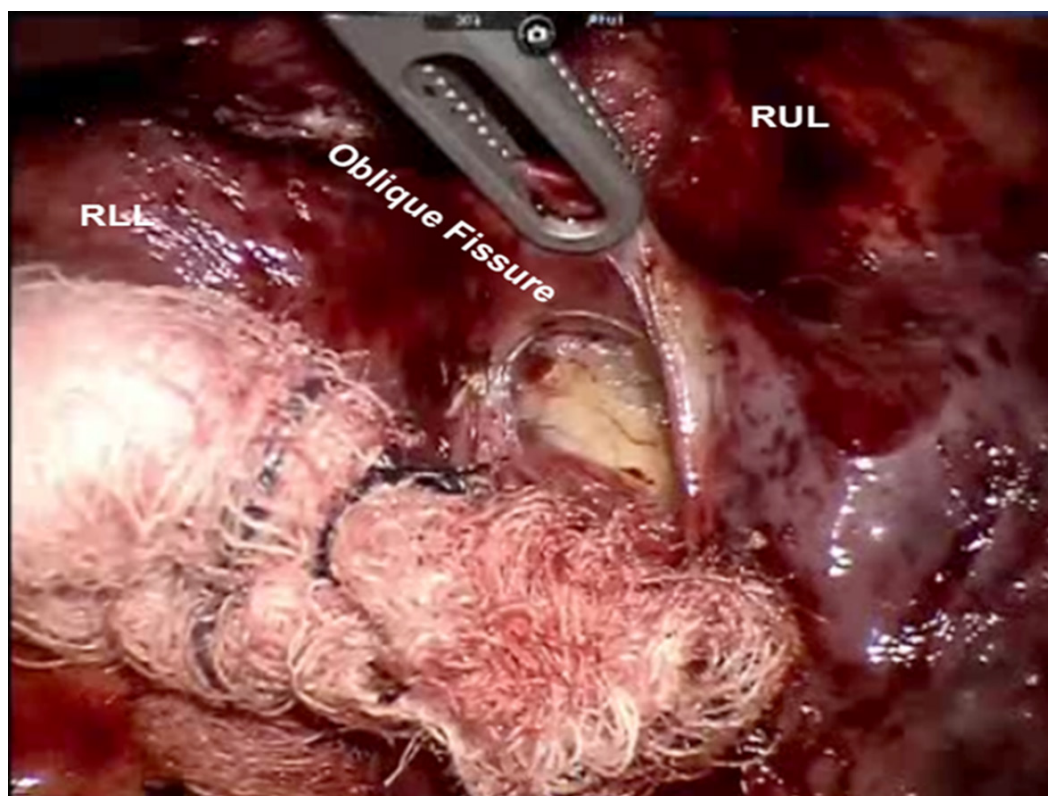


Figure 13. RS2 segmentectomy: Dissection is carried over the descending branch of the pulmonary artery under the posterior aspect of the oblique fissure and cephalad to the superior segmental pulmonary artery. RLL: right lower lobe; RUL: right upper lobe

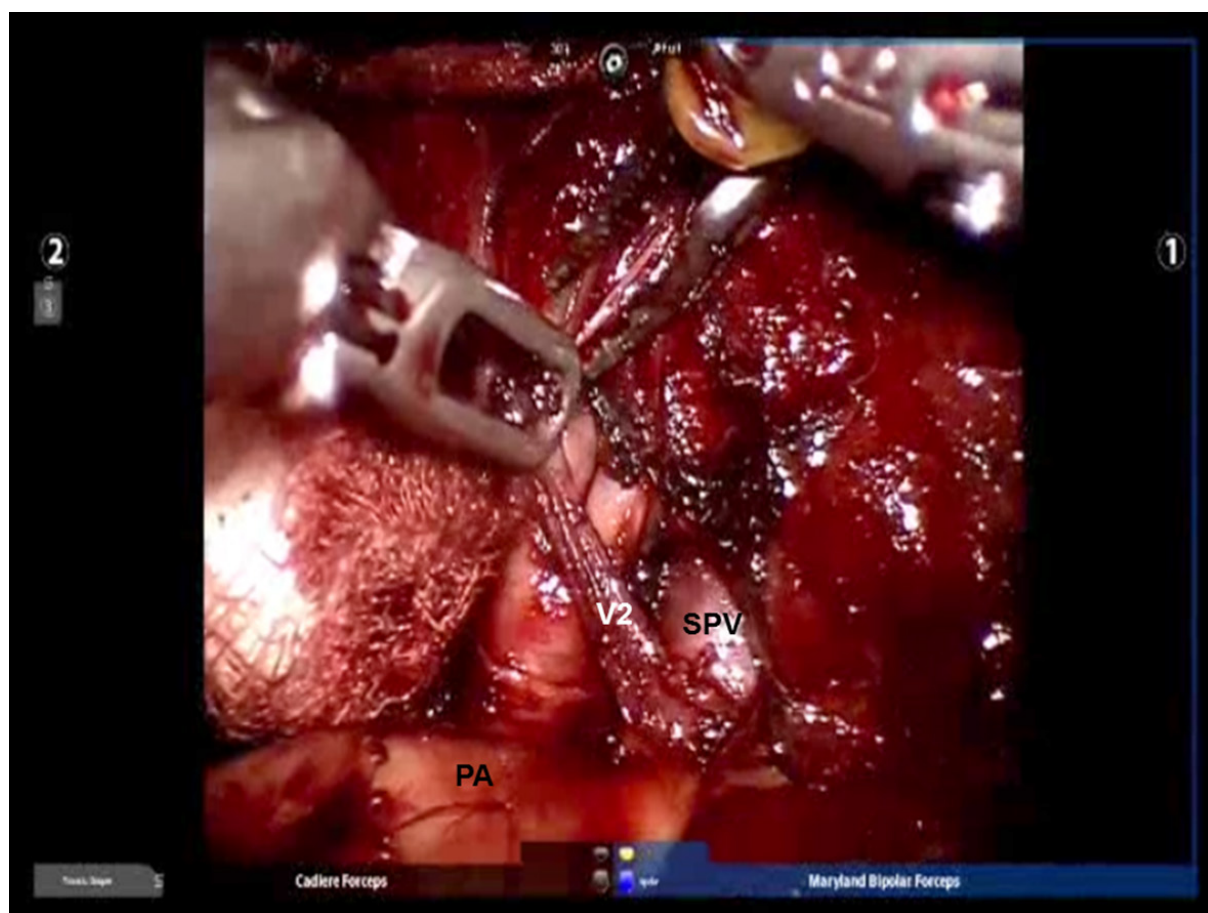


Figure 14. RS2 segmentectomy: The V2 vein runs posteriorly from the SPV in the oblique fissure. PA: pulmonary artery; SPV: superior pulmonary vein

the peribronchial N1 nodes are removed completely, the B2 bronchus is encircled with a vessel loop and divided with a stapler [Figure 15]. Finally, the intersegmental fissure is identified as described above and divided with a stapling device [Figure 16].

Right upper lobe anatomic anterior segmentectomy (S3)

Following the complete mediastinal nodal dissection and identification of the superior pulmonary vein, the descending trunk of the PA is approached in the oblique fissure. The nodes overlying the PA are removed. Dissection is carried cephalad in the sub adventitial plane, which overlies the PA toward the main trunk heading toward the space between the PA and superior pulmonary vein [Figure 17]. This maneuver elevates the transverse fissure of the lung away from the descending branch of the PA. A guide catheter is passed from a posterior to anterior direction under the transverse fissure, followed by a stapling device with a purple cartridge in the same direction, and the transverse fissure is divided. Division of the transverse fissure exposes the V3 pulmonary vein branches [Figure 18]. These are encircled with a vessel loop, elevated off of the PA emerging out of the pericardium, and divided using a stapler with a vascular cartridge. Next, the A3 PA branch is identified, encircled with a vessel loop, elevated, and divided using a stapling device [Figure 19]. The B3 bronchus emerges after dissecting the peribronchial N1 nodes that are between the PA and the bronchus [Figure 20]. The B3 bronchus is divided with a stapling device with a purple cartridge. Finally, the intersegmental fissure is identified as with the other segmentectomies and divided with a stapling device carrying a green cartridge [Figures 21 and 22].

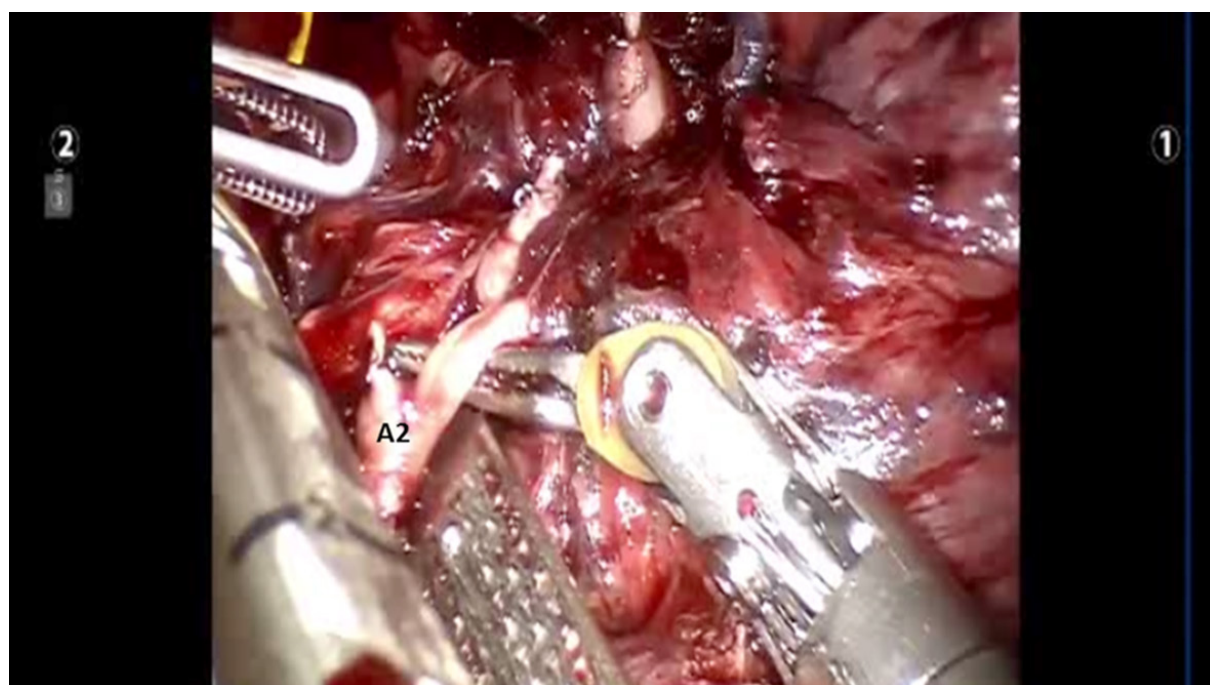


Figure 15. RS2 segmentectomy: Division of the V2 vein uncovers the A2 pulmonary artery branch

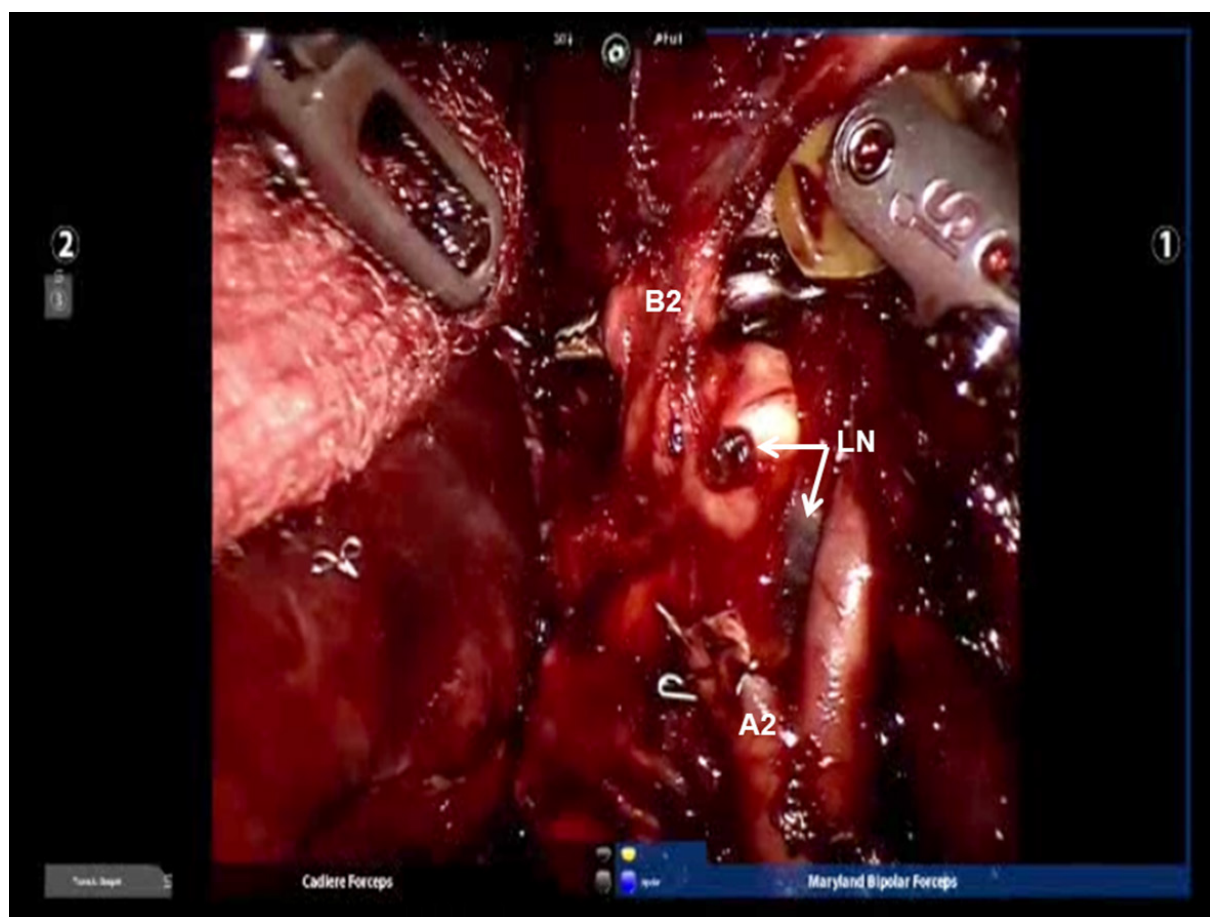


Figure 16. RS2 segmentectomy: The peribronchial N1 LN are removed completely, the B2 bronchus is encircled. The stapled stump of A2 branch of the pulmonary artery is seen. LN: lymph node

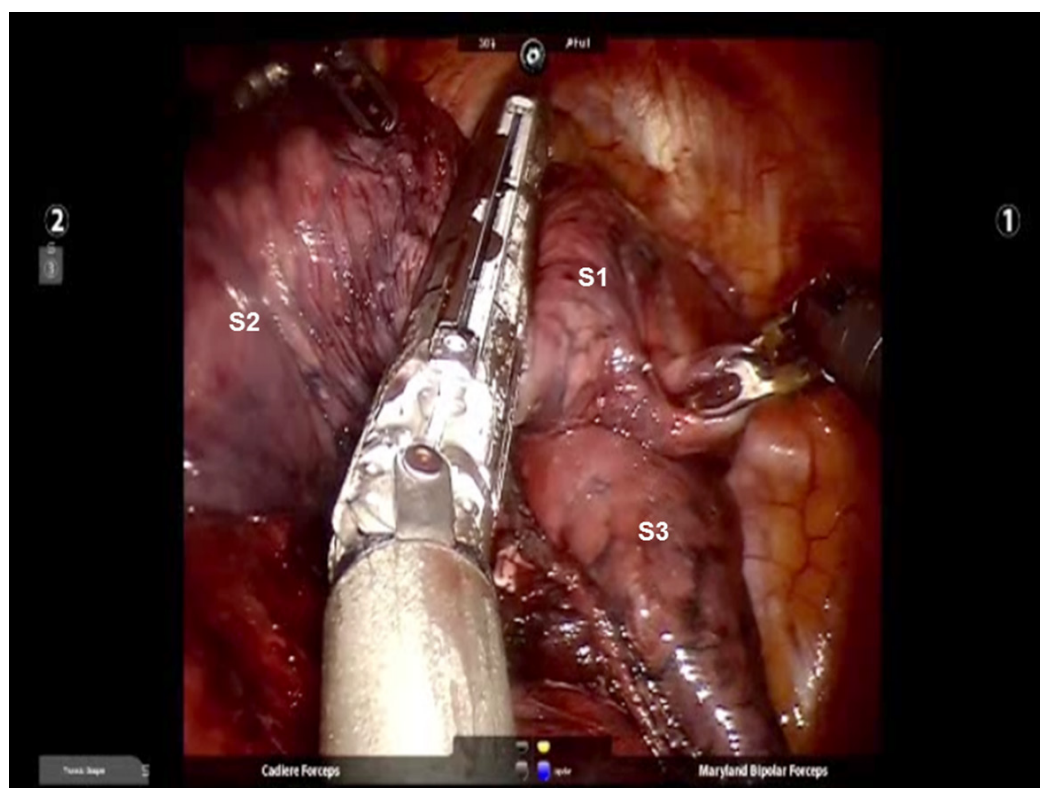


Figure 17. RS2 segmentectomy: The intersegmental fissure is identified by inflating the lung following the division of the B2 bronchus. The intersegmental fissure is divided with a stapling device. S1, S2, and S3 segments of the right upper lobe are seen

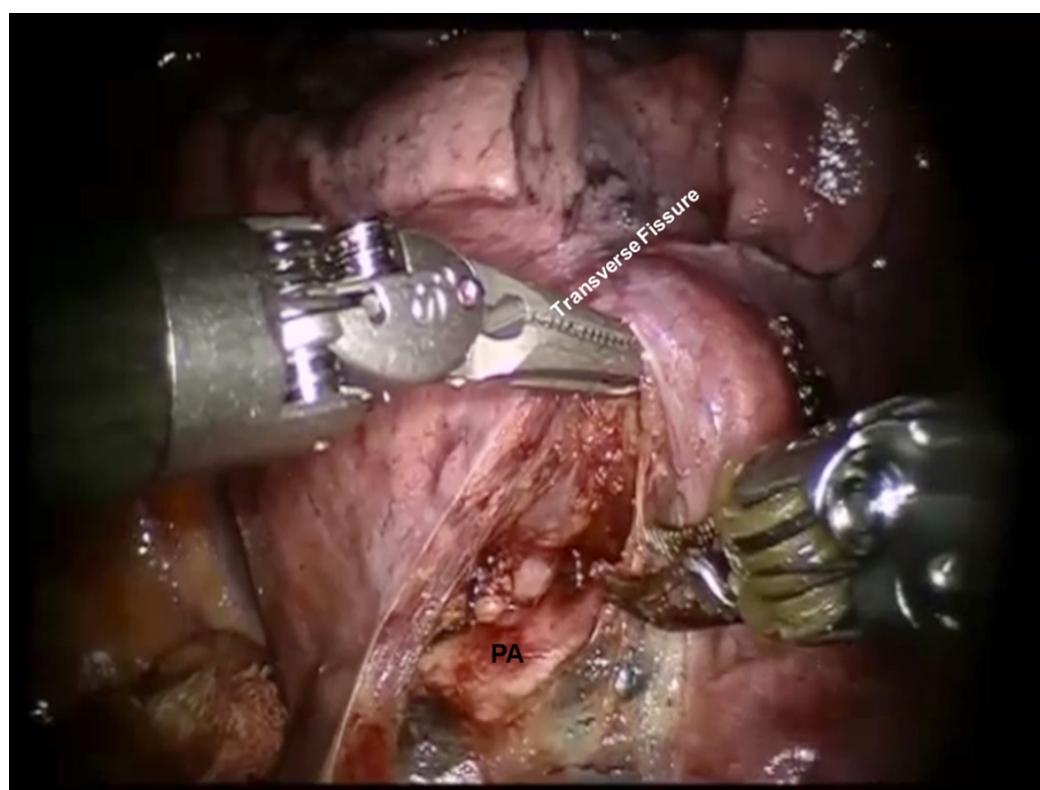


Figure 18. RS3 segmentectomy: The descending trunk of the PA is approached in the oblique fissure. Dissection is carried cephalad in the sub adventitial plane, which overlies the PA toward the main trunk heading toward the space between the pulmonary artery and superior pulmonary vein. PA: pulmonary artery

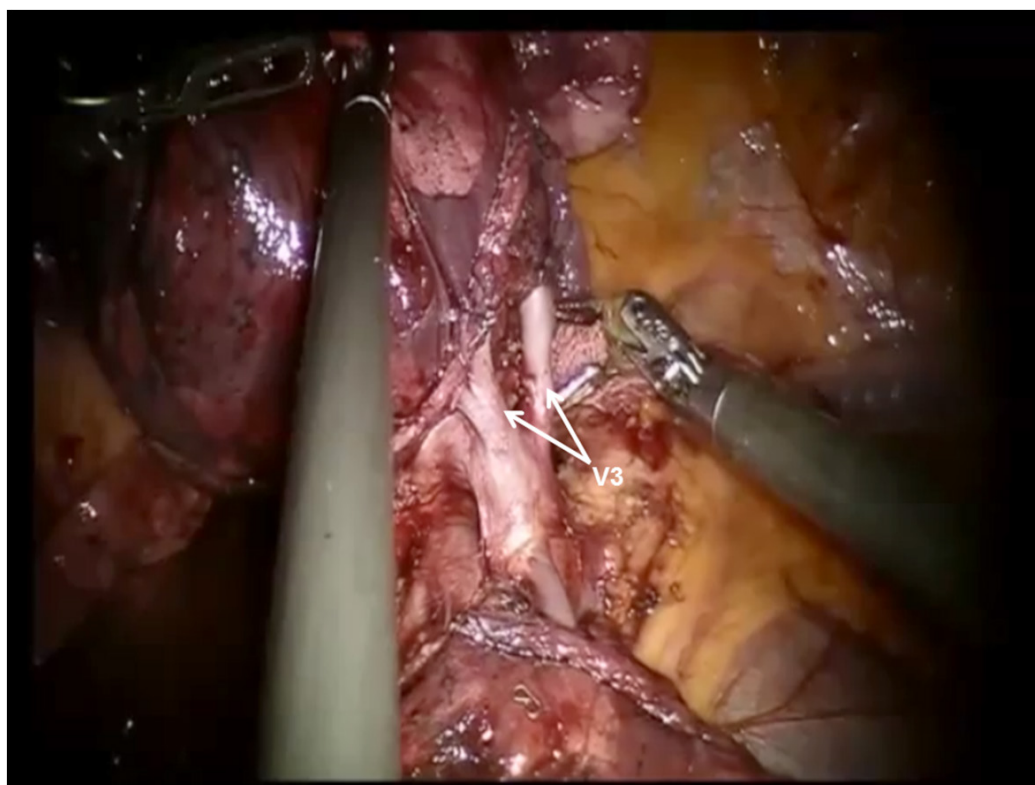


Figure 19. RS3 segmentectomy: Division of the transverse fissure exposes the V3 pulmonary vein branches

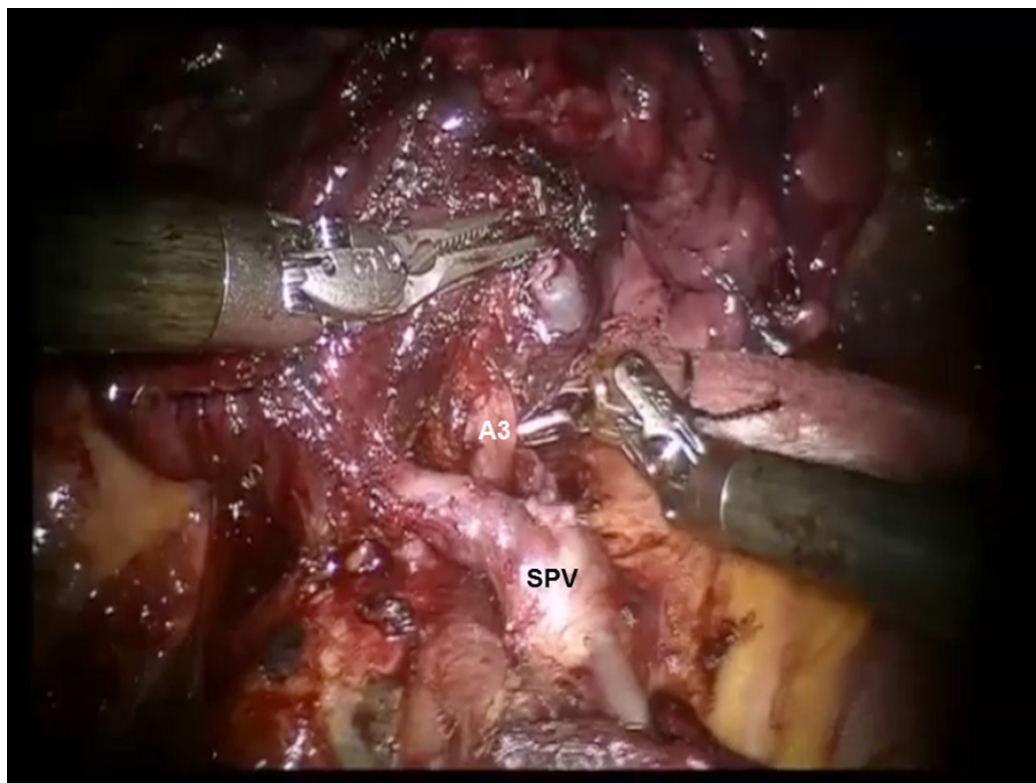


Figure 20. RS3 segmentectomy: Division of V3 exposes A3 branch of the pulmonary artery. SPV: superior pulmonary vein

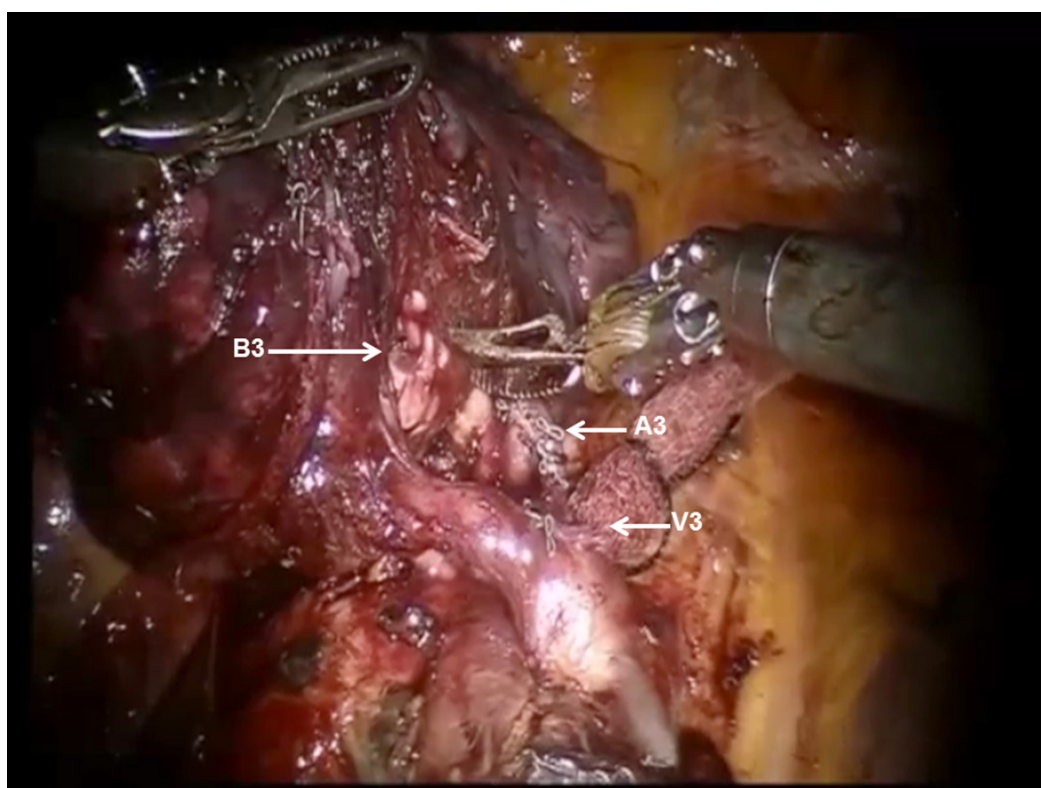


Figure 21. RS3 segmentectomy: The B3 bronchus emerges after dissecting the peribronchial N1 nodes that are between the pulmonary artery branch (A3) and the bronchus. The stapled stump of V3 pulmonary vein branch is seen

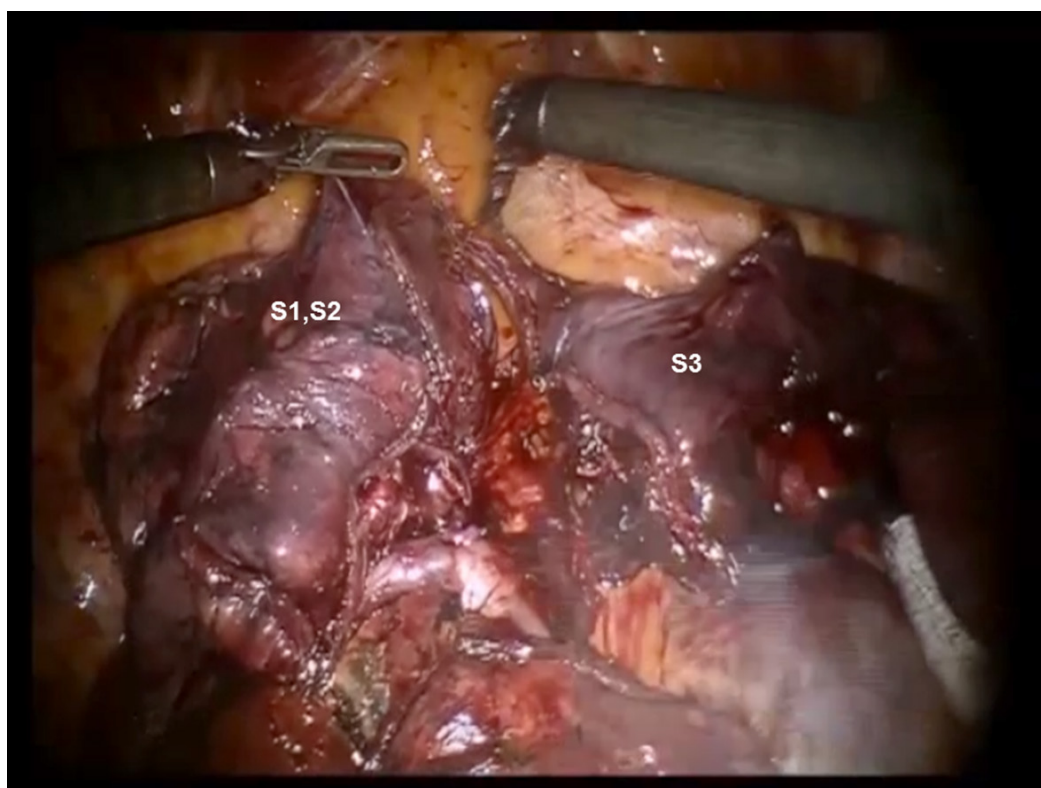


Figure 22. RS3 segmentectomy: Completed S3 segmentectomy. The separated S3 segment from S1 and S2 segments is seen

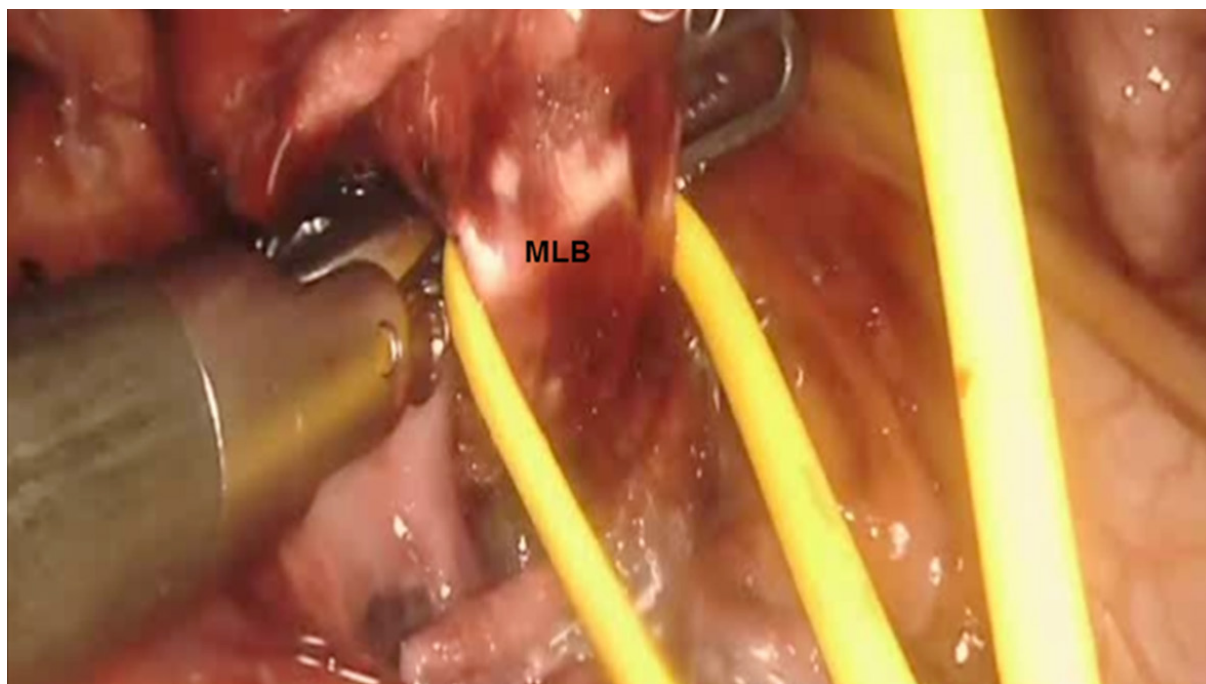


Figure 23. Right middle lobectomy (S4 and S5): The MLB is identified. MLB: middle lobe bronchus

Right middle lobe bi-segmentectomy (S4 and S5) = right middle lobectomy

Although segmentectomy of S4 and S5 is technically possible, conventionally, a right middle lobectomy is performed.

Completion of the lymph node dissection opens the mediastinal space and facilitates the dissection of the artery and the bronchus. The lobectomy begins with retraction of the lung laterally and posteriorly with the most posterior robot arm. This helps expose the hilum.

The pleura posterior to the phrenic nerve is incised. The superior pulmonary vein is dissected. The bifurcation between the right upper and middle lobar veins is developed by dissecting it off the underlying PA. The right middle lobe vein is encircled and divided [Figure 23].

In our experience, the best way to enter the appropriate plane over the PA is to follow the anterior segmental branch to the lower lobe. This branch is usually very superficial and is not covered with nodal or parenchymal tissue. This branch can be followed superiorly to the main PA. This maneuver helps to elevate Station #11 nodes off the PA and to identify the artery branch to the middle lobe. Next, the remainder of the fissure between the RML and RLL is divided in an anterior to posterior direction. At times, there is a vein branch to the middle lobe which drains into the inferior pulmonary vein. This is divided with the remainder of the anterior fissure.

Next, the middle lobe bronchus is identified [Figure 23]. It runs from left to right in the fissure. It is encircled and divided, taking care to avoid injuring the PA branches that are located directly behind it.

The middle lobe artery is encircled and divided with a vascular load. At times, the right middle lobe artery branches come off directly from the main PA instead of bifurcating from the common trunk of a single middle lobe artery. These are encircled and divided in the same fashion [Figure 24].

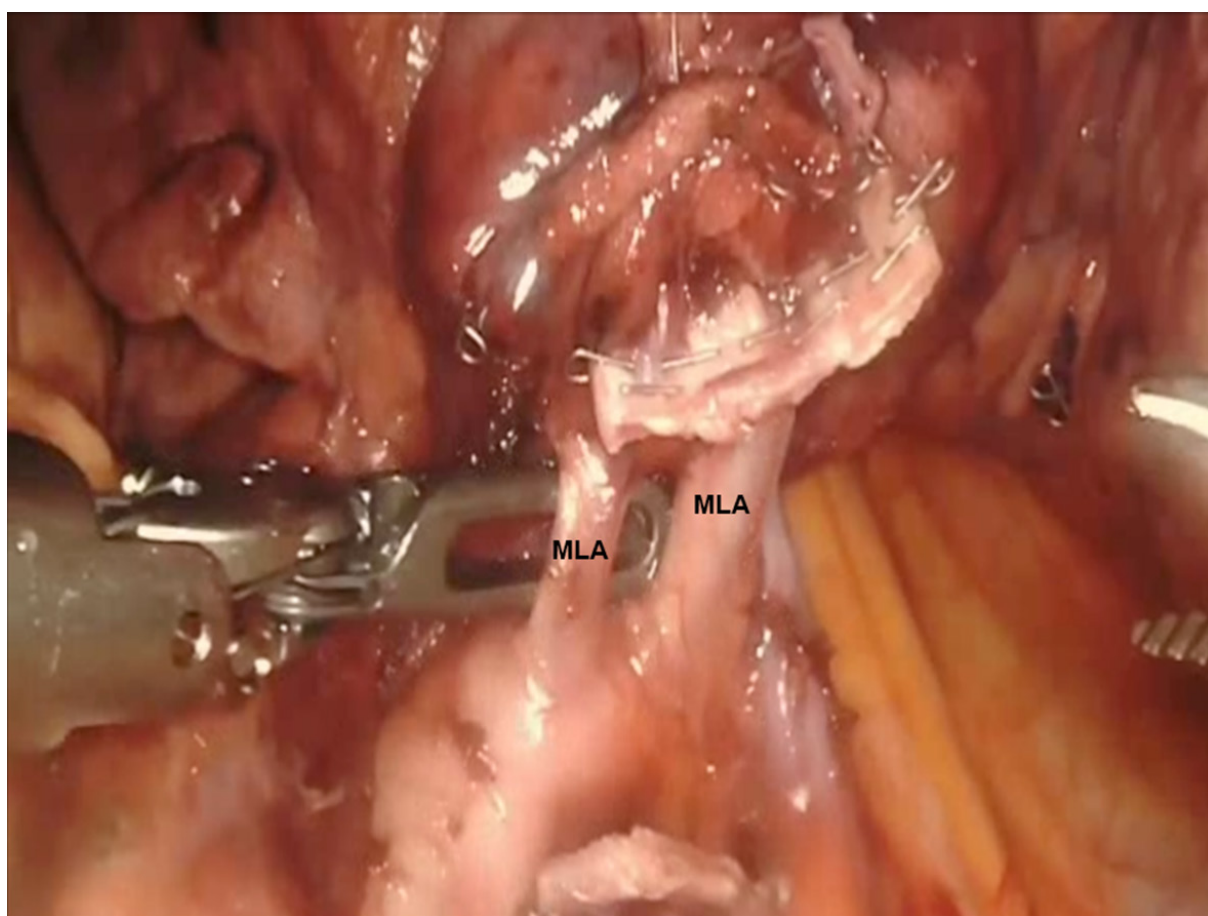


Figure 24. Right middle lobectomy (S4 and S5): The MLA are identified. MLA: middle lobe artery

Dissection of the fissure is then continued posteriorly until the main artery trunk and the superior segmental artery branch are identified. After identifying the main artery, the Cadiere Forceps in the left hand are used to go under the transverse fissure in a posterior to anterior direction heading for the divided superior pulmonary vein. A vessel loop is passed, and the fissure between the upper and middle lobes is divided using a stapler.

Right lower lobe anatomic superior segmentectomy (S6)

The docking, setup, and mediastinal nodal dissection is similar to right upper lobe anatomic segmentectomies.

The lung is retracted posteriorly and held in place with the robot arm. The bifurcation of the right superior and inferior pulmonary veins is dissected and delineated. The location of the right middle lobar vein should be positively identified to avoid inadvertent transection. The inferior pulmonary vein is encircled using the Cadiere Forceps.

The anterior branch of the lower lobe PA is most superficial and usually does not have overlying nodal tissue. This branch is identified and traced back to the main trunk of the PA. Next, the sub adventitial plane overlying the PA is developed and nodal tissue (Station #11) is removed. Retraction is released and the lung is allowed to remain in its normal position, thereby facilitating visualization of the oblique fissure. The dissection is carried out posteriorly in the sub adventitial layer and the superior segmental branch of the

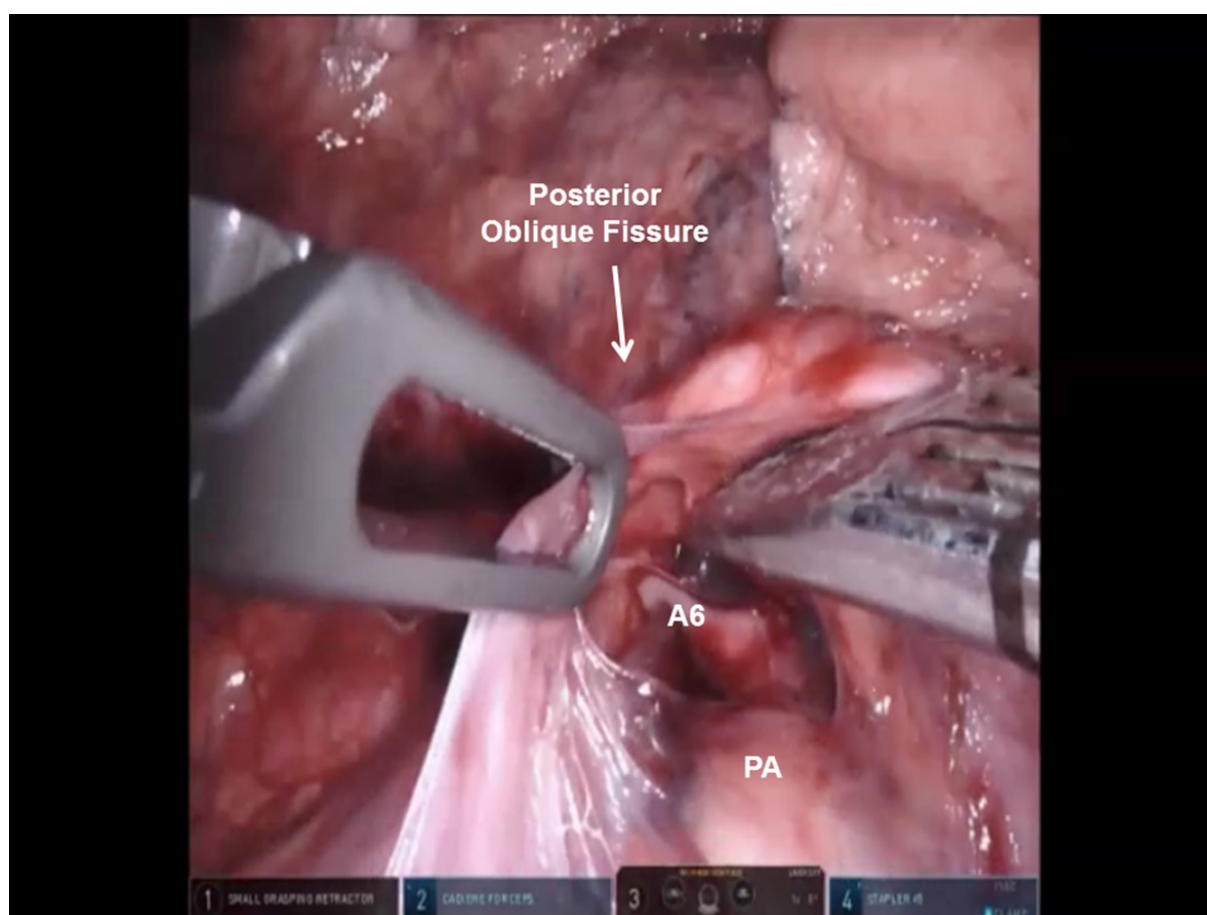


Figure 25. RS6 segmentectomy: The posterior oblique fissure is divided and the A6 branch of the descending PA is identified. PA: pulmonary artery

lower lobe PA is identified. The major fissure is then divided from an anterior to posterior direction using a stapler, which is introduced from the anterior port [Figure 25].

The A6 branch of the descending PA is identified, cleared of nodal tissue, encircled, and divided with a vascular stapler [Figure 26]. The nodes overlying the right lower lobe bronchus are swept toward the specimen, and the B6 bronchus is identified, encircled, and divided [Figure 27]. The intersegmental fissure between the S6 and the basal segments of the lower lobe is identified, as outlined above, and divided using a stapling device [Figure 28].

Right lower lobe anatomic basal segmentectomy (S7-S10)

Most surgeons would perform a formal lower lobectomy instead of a lower lobe basal segmentectomy. However, the approach to this segmentectomy is similar to superior segmentectomy (S6). Following the complete mediastinal nodal dissection and removal of Station #9, #7, #4L, #5, #10, and #11 nodes, the inferior pulmonary vein is encircled with a vessel loop and elevated. The superior segmental vein is identified, thereby allowing for identification of the basal branch of the inferior pulmonary vein. The basal vein is then divided with a stapling device with a white cartridge. Next, the PA is isolated in the fissure, as described above. The right lower lobe PA is identified, encircled, and elevated with a vessel loop. The basal branch of the right PA is divided with a vascular stapler. Following the division of the basal PA, the bronchus to the basal segment (B7-10) is encircled and divided with a stapler carrying a blue cartridge. Finally, the intersegmental fissure is identified and divided using a stapler with a green cartridge.

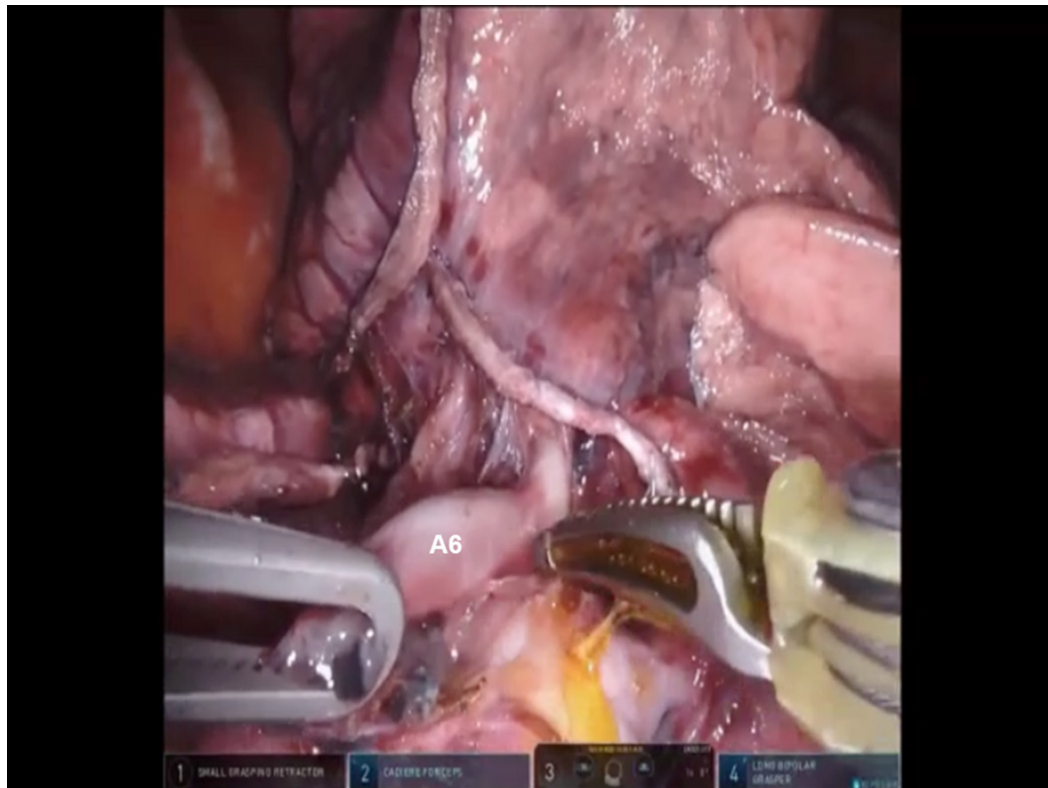


Figure 26. RS6 segmentectomy: The A6 branch of the descending pulmonary artery is skeletonized and divided

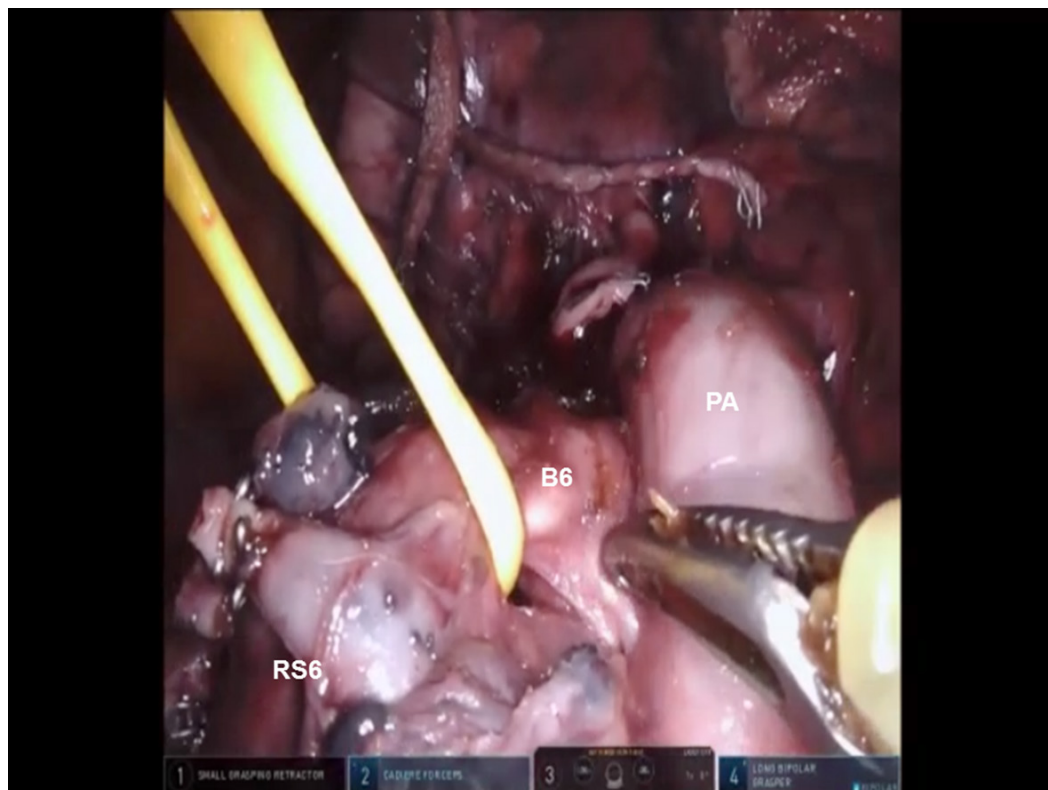


Figure 27. RS6 segmentectomy: B6 bronchus is identified and encircled prior to division. PA: pulmonary artery; RS: superior segment of right lower lobe

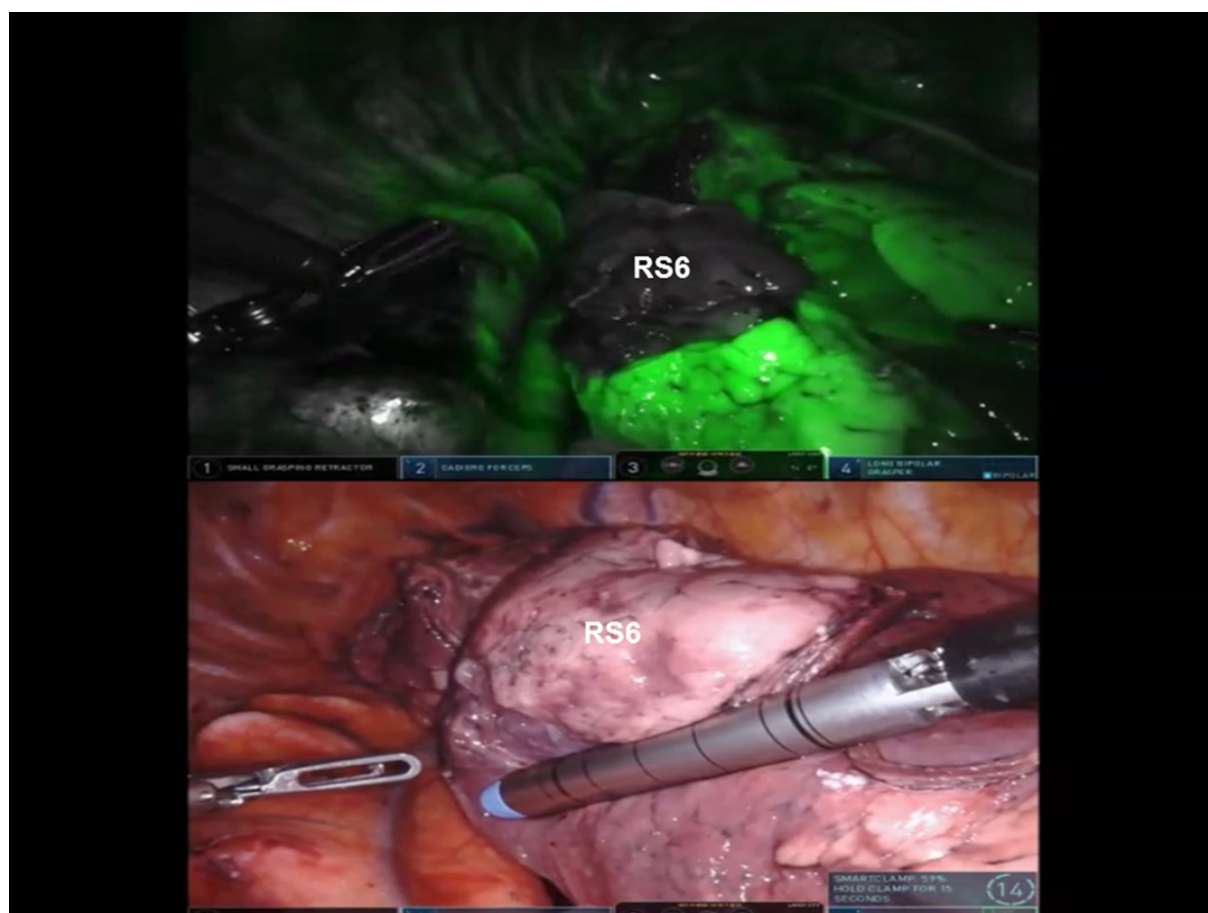


Figure 28. RS6 segmentectomy: The intersegmental fissure between the RS6 (superior segment right lower lobe) and the basal segments of the lower lobe is identified and divided

CONCLUSION

The surgical robot allows for precise dissection of the segmental bronchopulmonary structures, while minimizing trauma to surrounding tissues, and it allows for thorough and complete dissection of the mediastinal nodes. Robotic segmentectomy should be considered when planning a lung sparing operation in patients with smaller tumors or for physiologic considerations. The long-term results of robotic anatomic segmentectomy from our Institution were reported by Nguyen *et al.*^[19] Mean operative time was 134 min (range 70-227 min). Median length of stay was seven days (range 2-31 days). There were no conversions to robotic lobectomy. Two of 61 (3%) patients were converted to thoracotomy due to tumor location. Complications were minor (29%) with the most common being atrial fibrillation. There was no mortality. In patients with pathologic stage I NSCLC undergoing robotic anatomic segmentectomy, the lung cancer-specific five-year actuarial survival was 73%^[19].

The advantages of the use of robotic technology should be viewed in the perspective of increased cost and a steep learning curve for this complex procedure.

DECLARATIONS

Authors' contributions

Contributed equally to the performance of the surgeries, collection of data and writing the manuscript: Gharagozloo F, Meyer M

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

Open Access



The prognostic impact of frailty in patients undergoing percutaneous mitral valve repair

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Abstract

Aim: Percutaneous mitral valve repair (PMVR) with MitraClip® has proven to be an effective therapy to reduce mitral regurgitation in patients at high risk for conventional surgery. This population is currently characterized by advance age and high prevalence of comorbidities. Our aim was to evaluate the prevalence of frailty in a cohort of patients undergoing PMVR and its impact on clinical outcomes during follow-up.

Methods: A prospective registry was performed including all consecutive patients who underwent elective PMVR between June 2014 and March 2018 in our institution. Frailty was evaluated at admission with the functional FRAIL scale. In-hospital and 30-day procedural outcomes were collected. Clinical follow up was carried out including New York Heart Association (NYHA) functional class, heart failure hospitalization and death.

Results: Overall, 70 patients were included (mean age 75.3 ± 9.9 years, 65.7% male). Among them, 27 patients (38.6%) had a pre-procedural FRAIL score greater than 2, meeting frailty criteria. No differences between frail and non-frail patients were found in technical success ($P = 1.0$) or 30-day device success ($P = 0.739$). At six months follow up, both groups showed a significant improvement in NYHA functional class compared to baseline (frail: $P = 0.002$; non-frail: $P < 0.001$). During a median follow up of 675 (range 416-976) days, frailty patients had a higher incidence of HF admission and all-cause mortality ($P = 0.013$). In multivariate COX regression analysis, FRAIL score greater than 2 was significantly related to the primary composite endpoint (HR = 2.45; 95%CI: 1.02-5.88; $P = 0.044$).



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Conclusion: Frailty was common in patients undergoing PMVR in our institution. Despite post-procedural clinical improvement, frailty was related to adverse outcomes in our series.

Keywords: Percutaneous mitral valve repair, mitral regurgitation, frailty

INTRODUCTION

In the last decade, percutaneous mitral valve repair (PMVR) with MitraClip® device (Abbot Vascular, Santa Clara, USA) has proven to be an effective therapy to reduce mitral regurgitation (MR), with a low incidence of complications in patients deemed as high-risk candidates or unfit for conventional surgery^[1]. Risk stratification in these patients is challenging and it is usually based on non-dedicated risk scores developed in the surgery field, with a modest predictive value in this scenario^[2].

Frailty is a clinical syndrome related to aging and characterised by a decrease in so-called “biological reserve” against a stressful event, which implies a situation of vulnerability in the case of intercurrent disease or medical issues requiring hospitalization^[3]. Current candidates for PMVR are characterized by advanced age and a high prevalence of cardiovascular and non-cardiovascular comorbidities^[4,5]. All these factors have been commonly related to frailty. The main objective of our study was to assess the prevalence of frailty in a cohort of patients undergoing PMVR, and to assess its impact on clinical outcomes during follow-up.

METHODS

Study population

A prospective registry was performed including of all consecutive patients with symptomatic MR grade 3+ or 4+ who underwent elective PMVR in our center between June 2014 and March 2018. Those who received a MitraClip® as an urgent procedure ($n = 15$), during an admission for decompensated heart failure (HF), were excluded from the analysis.

Study procedures

The indications for PMVR in each patient were discussed by an interdisciplinary Heart Team, including clinical and interventional cardiologists, cardiac surgeons, and imaging specialists. Pre-procedural transthoracic and transesophageal echocardiography was performed in all patients to assess the severity of MR and the anatomical suitability for clip implantation, following current recommendations from the European Association of Cardiovascular Imaging for valvular heart disease assessment^[6]. PMVR was carried out under general anesthesia with guidance of fluoroscopy and transesophageal echocardiography.

Frailty was assessed according to functional FRAIL scale at admission for elective PMVR^[7]. The FRAIL questionnaire includes 5 components (Fatigue, Resistance, Ambulation, Illness and Loss of weight) and scores range from 0 to 5, considering as frail patients with score of 3-5. Baseline characteristics, echocardiographic and biochemical findings were collected. Procedural and 30-day clinical and echocardiographic outcomes were collected. New York Heart Association (NYHA) functional class was documented at the 6-month scheduled outpatient clinic after discharge. Long-term clinical follow-up was performed including primary re-admission for heart failure (HF) and death from any cause.

Study outcomes

Procedural results and adverse outcomes during follow-up were defined according to the “Mitral Valve Academic Research Consortium”^[8]. Technical success was defined as the implantation of at least 1 clip in the absence of procedural mortality or the need for emergency cardiovascular surgery. Device success at

30 days was defined as the implantation of at least 1 clip with residual MR $\leq 2+$ and transmitral valvular mean gradient < 5 mmHg, in the absence of major adverse events (death, stroke, unscheduled cardiovascular intervention, or device detachment). Device-related complications such as fracture, migration, embolization or partial detachment were considered as structural device failure. Functional failure was defined as the suboptimal result of PMVR during follow up (residual or recurrent MR 3+ or 4+ and/or transmitral mean gradient ≥ 5 mmHg). Anemia was defined according to the World Health Organization as a concentration of serum hemoglobin < 12 g/dL in women and < 13 g/dL in men^[9]. A composite primary endpoint of readmission for HF and all-cause death was established to define the prognostic impact of frailty in this series.

Statistical analysis

Continuous variables were summarized as mean \pm standard deviation or as medians and interquartile range, and were compared using unpaired Student *t*-tests or the non-parametric Wilcoxon rank sum tests if the normal distribution of the variables could not be demonstrated. Derangement from the normal distribution was assessed with the Shapiro-Wilk test. Categorical variables were described as percentages and compared using Chi-square or Fisher exact tests accordingly to expected frequency over or below 5, respectively. Survival curves for time-to-event were constructed on the basis of all available follow-up data using Kaplan-Meier estimates, and comparisons between frail and non-frail PMVR patients were performed using the log-rank test. Cox regression multivariate analysis was performed to evaluate the prognostic impact of frailty as an independent predictor for HF hospitalizations and all-cause mortality. Variables found to be statistically significant in the univariate analysis as well as others with clinical interest were included as covariates in the multivariable model. A *P*-value < 0.05 was regarded as statistically significant. Statistical analyses were performed using STATA software version 14.2.

RESULTS

In the study period, 70 patients (age 75.3 ± 9.9 years, 65.7% male) underwent elective PMVR in our center.

Study population

Baseline characteristics of patients included in the study cohort are summarized in Table 1, grouped by the presence of frailty criteria. Almost all patients (94.3%) had been admitted previously for HF, or were in advanced NYHA functional class III or IV. The etiology of the MR was predominantly functional, and patients were considered to be at high risk for conventional surgery according to surgical risk scales or Heart Team consensus. The prevalence of comorbidities was similar to other contemporary cohorts.

FRAIL questionnaire scores showed the following distribution in the cohort: score 0, 5.71%; score 1, 22.9%; score 2, 32.9%; score 3, 28.6%; score 4, 10.0%; score 5, 0%. Overall, 27 patients (38.6%) had a FRAIL score greater than 2, meeting frailty criteria. Patients classified as frail were older ($P = 0.043$), and had lower body mass index (0.030), higher prevalence of low serum albumin < 4 g/dL ($P = 0.046$), and anemia (0.046), higher number of admissions for HF in the previous year ($P = 0.044$), and worse prognosis estimated by Seattle HF risk score ($P = 0.005$). Likewise, they presented worse pre-procedural NYHA functional class ($P = 0.104$), higher levels of NT-proBNP ($P = 0.070$), and higher surgical risk ($P = 0.060$), as well as a higher prevalence of comorbidities (hypertension, advanced kidney disease, chronic obstructive pulmonary disease, or cognitive impairment), although this did not reach statistical significance.

Procedural results

At least one clip was successfully implanted in all patients, and 28 cases (40%) were treated with 2 or more clips. No significant differences were found in the duration of the procedure ($P = 0.749$), the time of fluoroscopy ($P = 0.768$), or the number of clips implanted between frail and non-frail patients ($P = 0.359$, Table 2). One patient (1.4%) underwent emergency valve replacement due to rupture of the subvalvular

Table 1. Baseline characteristics of patients included in the study cohort

All patients (n = 70)		Frail (n = 27)	Non frail (n = 43)	P value
Age (years)	75.3 ± 9.9	77.8 ± 9.0	73.7 ± 10.2	0.043
Male (%)	65.7	66.7	65.1	0.894
Body mass index (kg/m ²)	27.2 ± 5.5	25.6 ± 4.3	28.2 ± 6.0	0.030
Serum albumin < 4 g/dL (%)	44.3	59.3	34.9	0.046
Smoking (%)	40.0	44.4	37.2	0.548
Hypertension (%)	65.7	77.8	58.1	0.092
Diabetes (%)	27.1	25.9	27.9	0.856
Chronic obstructive pulmonary disease (%)	30.0	40.7	23.3	0.120
Glomerular filtrate rate ≤ 60 mL/min (%)	47.1	59.3	39.5	0.108
Peripheral arteriopathy (%)	22.9	29.6	18.6	0.285
Stroke (%)	14.3	18.5	11.6	0.493
Cognitive impairment (%)	7.1	14.8	2.3	0.069
Anemia (%)	44.3	59.3	34.9	0.046
Ischemic cardiopathy (%)	48.6	48.2	48.8	0.955
Acute myocardial infarction	31.4	37.0	27.9	0.423
Coronary revascularization	40.0	40.7	39.5	0.920
Percutaneous coronary intervention	34.3	33.3	34.9	0.894
Coronary artery bypass grafting	14.3	18.5	11.6	0.423
Non-coronary cardiac surgery (%)	14.3	11.1	16.3	0.730
Implantable cardiac device (%)	31.4	22.2	37.2	0.189
Atrial fibrillation (%)	62.9	66.7	60.5	0.601
Left ventricular ejection fraction (%)	40.5 ± 16.3	41.1 ± 16.9	40.1 ± 16.1	0.597
Mitral regurgitation (%)				1.0
3+	10.0	11.1	9.3	
4+	90.0	88.9	90.7	
Etiology of mitral regurgitation (%)				0.298
Degenerative or mixed	27.1	33.3	23.3	
Ischemic functional	35.7	40.7	32.6	
Non-ischemic	37.1	25.9	44.2	
Severe pulmonary hypertension (%)	22.9	29.6	18.6	0.285
Prior heart failure admission within 12 months	1 [1-2]	2 [1-3]	1 [1-2]	0.044
NYHA functional class (%)				0.104
II	18.6	14.8	20.9	
III	67.1	59.3	72.1	
IV	14.3	25.9	7.0	
NT-pro brain natriuretic peptide (pg/mL)	2030.5 [1126.0-3428.0]	2962.0 [1525.0-9059.0]	2030.5 [1126.0-3428.0]	0.070
Euro score logistic (%)	17.4 [10.1-30.3]	21.6 [11.1-36.9]	16.0 [9.2-29.2]	0.151
Society of thoracic surgeons (%)	3.6 [1.9-5.4]	4.2 [2.4-6.1]	2.8 [1.2-5.4]	0.060
Seattle heart failure risk score (%)	16.6 [10.5-20.3]	19.8 [14.0-30.6]	15.4 [8.4-19.5]	0.005

NYHA: New York Heart Association

apparatus with massive residual MR after MitraClip® deployment. Overall, procedural technical success was 98.6%, with no differences between the two groups ($P = 1.0$). Likewise, no significant differences in the incidence of major procedural complications were observed during hospitalization.

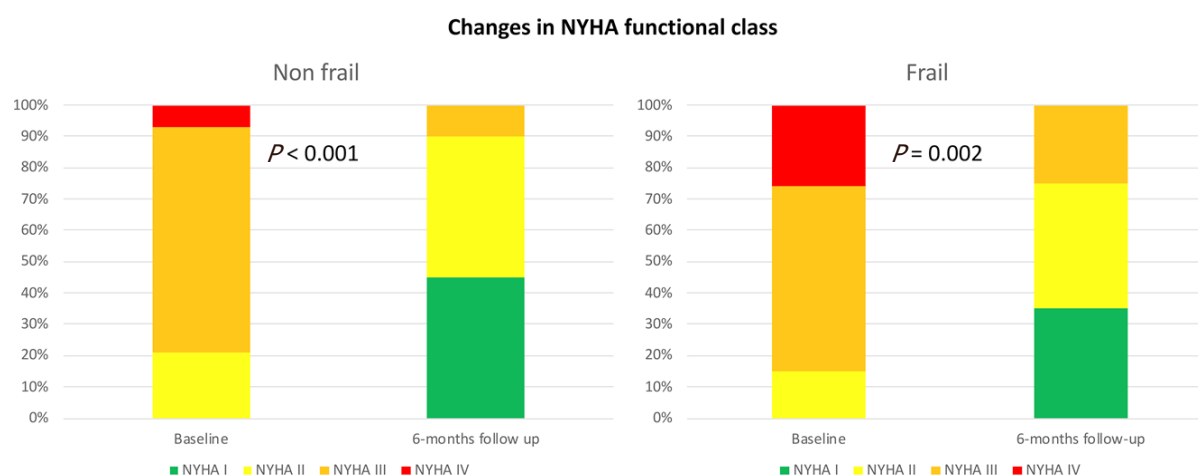
At 30-day echocardiographic follow-up, one patient (1.4%) had partial clip detachment with severe residual MR, and 6 patients (8.6%) had residual MR > 2+ and/or transmitral mean gradient ≥ 5 mmHg. One patient with very severe left ventricular dysfunction died within 30 days after discharge. Overall, device success rate at 30 days was 84.3%, with no differences between frail and non-frail groups ($P = 0.739$).

Clinical outcomes

At 6-month follow up, both groups of patients showed a significant improvement in NYHA functional class (frail: $P = 0.002$; non-frail: $P < 0.001$; [Figure 1](#)). During a median follow-up of 675 days (range 416-976), 22 patients (31.4%) were hospitalized due to HF and 16 patients (22.9%) died. The composite endpoint of readmission for HF or death from any cause occurred in 30 patients (42.9%).

Table 2. Short-term procedural outcomes

All patients (n = 70)		Frail (n = 27)	Non frail (n = 43)	P value
Procedure	Days of admission	4 [4-5]	4 [4-5]	0.625
	Device time (min)	62.5 [45.0-86.0]	70.0 [42.0-95.0]	0.749
	Fluoroscopy time (min)	40.8 [34.3-50.0]	43.4 [34.4-54.0]	0.768
	Number of clips	1 [1-2]	1 [1-2]	0.359
	Emergent cardiac surgery (%)	1.4	2.3	1.0
30-day	Procedural death (%)	0	0	1.0
	Technical success (%)	98.6	100	1.0
	Cardiovascular intervention (%)	4.3	7.0	0.279
	Stroke (%)	0	0	1.0
	Transient ischemic attack (%)	2.9	2.3	
	Major vascular complication (%)	2.9	2.3	1.0
	Major structural complication (%)	0	0	1.0
	Major bleeding (%)	7.1	4.7	0.367
	Life-threatening or fatal bleeding (%)	0	0	1.0
	Acute kidney injury grade 2 or 3 (%)	0	0	1.0
	Death (%)	1.4	0	0.386
	Structural failure (%)	1.4	0	0.386
	Functional failure (%)	8.6	7.0	0.670
	Device success (%)	84.3	86.1	0.739

**Figure 1.** Changes in NYHA functional class according to frailty status. NYHA: New York Heart Association

Frail patients had a non-significantly higher rate of HF hospitalization (log-rank test: $P = 0.080$, Figure 2A), and a lower survival (log-rank test: $P = 0.006$, Figure 2B), compared to non-frail patients. Survival free of the composite endpoint was significantly lower in the group of frail patients (log-rank test: $P = 0.013$, Figure 2C), with a probability of survival with no HF re-admission at one-year follow up of 61.6% vs. 83.7% in frail and non-frail patients, respectively.

In Cox regression analysis, frailty was significantly related to the composite endpoint in the univariate analysis (HR = 2.59; 95%CI: 1.24-5.41; $P = 0.011$). This association was not significantly modified (HR = 2.45; 95%CI: 1.02-5.88; $P = 0.044$) after adjusting in a multivariate model including the following variables: age, diabetes mellitus, advanced chronic kidney disease (stage IIIb-V), pre-procedural NYHA functional class, high Seattle HF risk score, and atrial fibrillation.

DISCUSSION

This study analyzed the prevalence of frailty in a single-center cohort of patients undergoing elective PMVR, and its impact on clinical outcomes during a median follow-up over 1 year. The main findings of

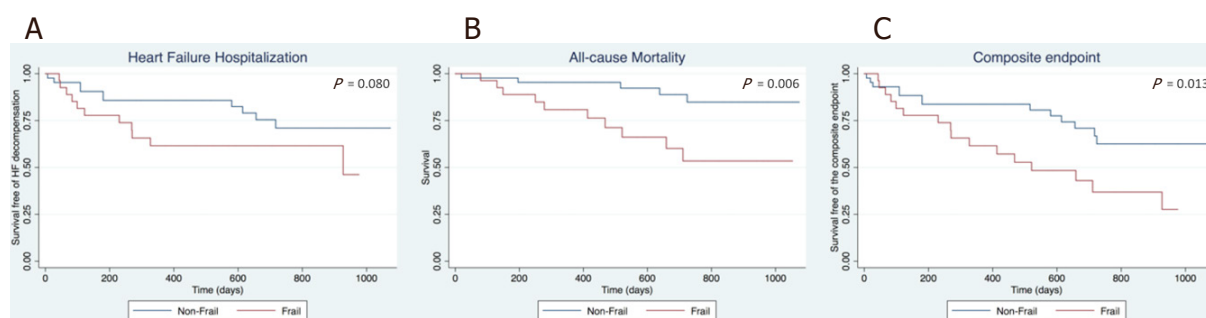


Figure 2. Kaplan-Meier curves displaying survival free from heart failure or death. A: Heart failure rehospitalizations. Frail patients experienced higher prevalence during follow-up; B: All cause mortality. Frail patients showed higher death rate than non frail patients; C: Composite end-point (death/readmission due to heart failure). Frail patients showed worse outcome.

our report were the following: (1) the prevalence of frailty in this series was high (about 2 out of 5 patients); (2) no differences in procedural outcomes and short-term device success rates were observed between frail and non-frail patients; (3) NYHA functional class significantly improved in both groups at 6-months follow-up after PMVR; and (4) frailty was significantly related to a higher risk of HF readmission or death from any cause during long-term follow-up.

Prevalence of frailty among patients with cardiovascular disease ranges between 25% to 50%, depending on the scales used and the clinical setting^[10]. In addition, many reports have shown a higher incidence of adverse events in frailty patients with ischemic heart disease, HF, or those undergoing cardiac surgery, or percutaneous intervention for either coronary or structural heart disease^[11-14]. In the latter scenario, several studies have pointed out that patients deemed as frail who undergo percutaneous aortic valve replacement have worse prognosis than those that do not meet frailty criteria^[14,15]. Similar findings have been reported in patients undergoing PMVR. In this regard, Metze *et al.*^[16] observed a prevalence of frailty according to the FRIED score of 45.5% in a cohort of more than 200 patients who received MitraClip®. In this series, device success rates were similar among frail and non-frail patients, and a significant improvement was observed in both groups in the NYHA functional class, 6-min walk test, and quality of life questionnaires. However, frailty was significantly related to a higher probability of readmission for HF or death from any cause during a median follow-up of more than 1 year. Likewise, in our study, the presence of frailty according to the FRAIL score was associated with a more than two-fold increase in the incidence of the composite endpoint, despite similar short-term procedural results and functional improvement.

Multiple frailty scales have been validated in different clinical settings^[3]. Some, such as the FRIED score, focus on physical strength and walking speed. This “uni-dimensional” approach has a higher predictive value in some scenarios of cardiovascular disease, although their use in daily practice is limited by its greater complexity and time demands^[17]. On the other hand, the “multidimensional” approach, including the FRAIL scale, considers that frailty is an accumulation of comorbidities, deficits and symptoms involving one or more domains of human functioning. These scores are based on clinical questionnaires and the subjective judgment of the healthcare provider. The advantages of this approach are that it is simple to perform and can be used in patients with any stage of disability as a screening test. To the best of our knowledge, this is the first study to evaluate the prognosis impact of the FRAIL score in PMVR.

In between both scores, a modified FRAIL scale has been recently suggested, adding a rapid physical test (e.g., the ability to get up from the chair), a questionnaire to address cognitive impairment, and two laboratory parameters (serum albumin and hemoglobin) to the traditional score^[14]. This “Essential Frailty Toolkit” demonstrated a greater predictive value for adverse events compared to other scales in patients with severe aortic stenosis undergoing either surgical or percutaneous valve replacement. Further studies

are needed to assess its usefulness in patients undergoing other structural interventional procedures.

PMVR with MitraClip® has proven to persistently reduce MR with low rates of procedural complications in patients at high surgical risk^[18]. Furthermore, observational registries have shown a significant improvement in functional class, 6-minute walk test and quality of life^[19]. More recently, data from randomized controlled trials suggest that there might be a survival benefit of MitraClip® compared to stand-alone medical therapy in patients with functional MR^[20-22]. Nevertheless, selection of patients in order to find those who will benefit the most from PMVR and avoid futility is still extremely challenging. In this regard, pre-procedural evaluation of frailty might help to identify those patients with very poor short-term prognosis and those at a higher risk of non-cardiovascular mortality^[23]. Although there is extensive evidence of the prognosis impact of frailty in cardiovascular disease, some aspects should be taken into account. First, frailty, in the absence of advanced disability, is a potentially reversible and treatable condition, so that a pre-procedural intervention could hypothetically improve the clinical prognosis of patients at high risk^[24]. Second, the latest recommendations of the geriatric societies do not consider frailty as a contraindication to any invasive treatment but, on the contrary, as an important assessment element to establish an individualized plan of care^[3]. Therefore, frailty should be an additive point to address by the multidisciplinary Heart Team when considering a potential candidate for MitraClip®, never a single tool for decision making. Risk stratification of patients undergoing PMVR is currently based on non-dedicated scales developed in the surgical field with a modest power of discrimination in this scenario^[2]. The implementation of frailty scales might improve selection of patients^[25]. Finally, despite an worse prognosis, frail patients showed a significant clinical improvement in the short-term and, therefore, this therapy might be considered for symptomatic relief in the absence of other reliable alternatives, even in the absence of consistent survival benefit.

Limitations

This study has some limitations. First of all, it is a single center small cohort of patients. Second, no dedicated test has been included to assess physical frailty, such as pressure force or gait speed. Third, frailty was not re-evaluated during follow up.

In conclusion, frailty was a frequent finding among patients undergoing PMVR. The presence of this syndrome did not impact procedural success. Despite symptomatic improvement in this patient group after PMVR, frailty was associated with an increase in adverse outcomes during follow-up. Further studies are needed to validate our results, and to assess whether any intervention to improve this syndrome can modify the prognosis of this patient group.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Benito-González T, Estévez-Loureiro R

Performed data acquisition, as well as provided administrative, technical, and material support: del Castillo S, Minguito-Carazo C, Echarte-Morales J, Garrote-Coloma C

Drafted the paper: Benito-González T, Estévez-Loureiro R, Garrote-Coloma C

Reviewed critically: Fernández-Vázquez F

Gave final approval: Benito-González T, Estévez-Loureiro R, del Castillo S, Minguito-Carazo C, Echarte-Morales J, Garrote-Coloma C, Fernández-Vázquez F

Availability of data and materials

Data of this work can be provided in case of formal request and under a legitimate cause.

Financial support and sponsorship

None.

Conflicts of interest

Benito-González T received an unrestricted research grant from Abbot Vascular not related to this report; Estévez-Loureiro R and Garrote-Coloma C are proctors for MitraClip®.

Ethical approval and consent to participate

This research has been conducted in accordance with the Declaration of Helsinki and approved by University Hospital of Leon ethics committee. All participants gave informed consent.

Consent for publication

Not applicable.

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Review

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The technique of robotic anatomic pulmonary segmentectomy II: left sided segments

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Abstract

Anatomic pulmonary segmentectomy and mediastinal nodal dissection has been advocated in patients with smaller tumors or patients with limited pulmonary reserve. The overall 5-year survival and the lung cancer-specific 5-year survival following anatomic segmentectomy have been shown to be equivalent to that of lobectomy. Robotic surgical systems have the advantage of magnified, high-definition three-dimensional visualization and greater instrument maneuverability in a minimally invasive platform. These robotic systems can facilitate the dissection of the bronchovascular structures and replicate the technique of segmentectomy by thoracotomy. Greater experience with the robotic platform has resulted in a reproducible anatomic segmentectomy technique. This is a companion paper to The Technique of Robotic Anatomic Segmentectomy I: Right Sided Segments. This paper outlines the technique of anatomic pulmonary segmentectomy for the left lung: Left Upper Lobe (LUL) Anterior Segment (S3), LUL Apicoposterior Segment (S1 + S2), LUL Lingulectomy (S4, S5), Left Lower Lobe (LLL) Superior Segmentectomy (S6), and LLL Basal Segmentectomy (S7-S10).

Keywords: Robotic, segmentectomy, lung cancer, superior segment, anterior segment, apicoposterior segment, basal segment, sublobar resection

INTRODUCTION

Historically, anatomic pulmonary segmentectomy was used for the surgical treatment of lung abscesses and other lung infections. Chevalier Jackson and John Hubert first proposed a system of nomenclature for the



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bronchopulmonary segments^[1]. In 1939, Churchill and Belsey^[2] reported the first anatomic segmentectomy, a lingulectomy. Edward Boyden described the vascular and bronchial anatomy for pulmonary segments^[3].

In the latter half of the twentieth century, the advent of antibiotic therapy led to a decrease in segmentectomies performed for infectious lung processes and an increase in their use for primary malignancies of the lung. In the 1960's and 1970's, Rasmussen and Clagett published reports of segmentectomy for lung cancer with low mortality^[4]. With the introduction of stapling devices in the late 1960's, wedge resections, which were technically much easier, became widely used. Thereafter and unfortunately, wedge resection, a nonanatomic pulmonary resection, and individual ligation anatomic segmentectomy became grouped as "sublobar resections". Subsequent studies showed that anatomic segmentectomy was associated with significantly better cancer-related survival than wedge resection^[5]. However, as anatomic segmentectomy is a technically more demanding procedure than lobectomy, lobectomy became the procedure of choice for early stage lung cancer.

Recently, anatomic pulmonary segmentectomy has been shown to be a viable oncologic procedure for early lung cancer, including patients who are elderly or have limited pulmonary reserve^[6-14]. As a result of high definition three-dimensional visualization and increased maneuverability of the surgical instruments in a small space, the surgical robot has the distinct advantage of replicating the technique of anatomic segmentectomy by thoracotomy using a minimally invasive platform^[15]. Although there has been skepticism about the cost and the lack of evidence of the survival advantage of using robotic lobectomy, the robotic platform seems to be especially suited to a minimally invasive approach to anatomic segmentectomy^[15,16]. Greater experience with the robotic platform has resulted in a reproducible anatomic segmentectomy technique.

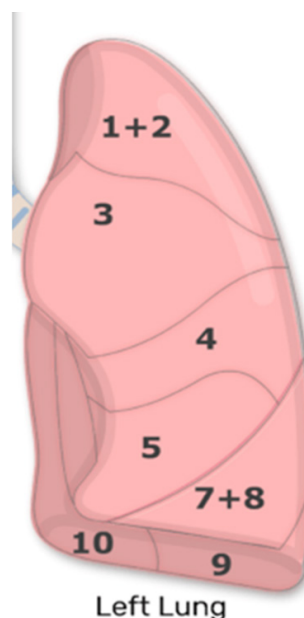
This is a companion paper to The Technique of Robotic Anatomic Segmentectomy I: Right Sided Segments. This paper outlines the technique of anatomic pulmonary segmentectomy for the left lung: Left Upper Lobe (LUL) Anterior Segment (S3), LUL Apicoposterior Segment (S1 + S2), LUL Lingulectomy (S4, S5), Left Lower Lobe (LLL) Superior Segmentectomy (S6), and LLL Basal Segmentectomy (S7-S10).

ANATOMIC SEGMENTECTOMY IN THE LEFT LUNG

The bronchopulmonary segments of the left lower lobe are similar to the right lower lobe. Although there are only two lobes in the left lung, there is some symmetry among the bronchopulmonary segments bilaterally. However, some segments of the left lung merge, resulting in fewer bronchopulmonary segments on the left than there are on the right lung [Figure 1].

The apicoposterior segment (S1 + S2) of the left upper lobe represents the fusion of the apical and posterior segments. Although the Lingula is divided into two bronchopulmonary segments, the superior (S4) and inferior (S5) Lingular segments, from a practical standpoint, S4 + S5 segmentectomy or lingulectomy is typically performed. In the left lower lobe, there are four segments unlike the right lower lobe which has five segments. The anteromedial basal segment (S7 + S8) represents the fusion of the anterior basal and medial basal segments. The other segments (superior S6, posterior basal S10, and lateral basal S9) maintain the same relative positions as observed in the right lung.

From a surgical standpoint, sublobar resection is usually performed for LUL anterior segment (S3), LUL apicoposterior segment (S1 + S2), LUL lingulectomy (S4, S5), LLL superior segmentectomy (S6), and LLL basal segmentectomy (S7-S10). It is possible to perform individual anatomic segmentectomy of the basal segments S7 + S8, S9, or S10. We have no experience with robotic segmentectomy of these individual basal segments and therefore have not included them in this report.

Upper Lobe*Apico-posterior (LS1,2)**Anterior (LS3)**Superior lingular (LS4)**Inferior lingular (LS5)***Lower Lobe***Superior (LS6) (on posterior surface)**Anterio-medial basal (LS7,8)**Lateral basal (LS9)**Posterior basal (LS10)***Figure 1.** Bronchopulmonary segments of the left lung**Port placement**

The operating room table is reversed such that the pedestal does not interfere with the docking of the robot over the head of the patient.

A double lumen endotracheal tube is placed, and the patient is positioned in a full lateral decubitus position. The left arm is placed over pillows and positioned high enough such that access to the 4th intercostal space in the anterior axillary line is readily attained. The table is flexed in order to move the hip down and to open the intercostal spaces. The lung is deflated and placed on suction. The position of the double lumen tube is rechecked after the patient is prepped and draped. We prefer the use of a double lumen tube as opposed to a bronchial blocker. During robotic dissection, manipulation of the hilum and the bronchus can result in dislodgement of the blocker and loss of lung isolation. Every effort should be made to ensure lung isolation for the entire procedure. The position of the robot over the head of the patient makes manipulation of the endotracheal tube difficult. Untimely inflation of the lung can result in loss of exposure and its associated complications.

Proper port positioning is crucial and a fundamental prerequisite to the conduct of the procedure. [Figures 2 and 3](#) show port placements. A line is drawn from the tip of the scapula to the costal arch. This delineates the highest point in the chest and the midscapular line (posterior axillary line). Pleural entry is with a Hassan needle. Saline is infused and care is taken to look for easy egress of the saline from the needle. If there is concern of pleural adhesions, we use a Visiport Instrument (Medtronic Inc. Norwalk, CT) for entry into the pleural space under direct vision. If the Visiport is used, a purse string is placed in the muscle layer and tied around the robot camera port in order to prevent CO₂ leakage. Port #1 is the camera port. Warm, humidified CO₂ is insufflated through this port at a flow rate of 6 L/min to a pressure of 6-8 mmHg in order to push the lung and diaphragm away. The other ports are placed under direct vision. Port #2 is placed in the 7th intercostal space in the posterior scapular line. This port is 9 cm posterior to Port #1. Prior to the placement of Port #3, a 21-gauge needle is inserted into the 7th intercostal space at costovertebral junction from the patient's back and a 10 mL subpleural bubble of 0.25% bupivacaine with epinephrine is injected near the intercostal nerve. Next, Port #3 is placed 9 cm posterior to Port #2 in the 7th intercostal space just medial to the spine. Port #4 is placed 9 cm anterior to Port #1 in the 7th intercostal space at the anterior

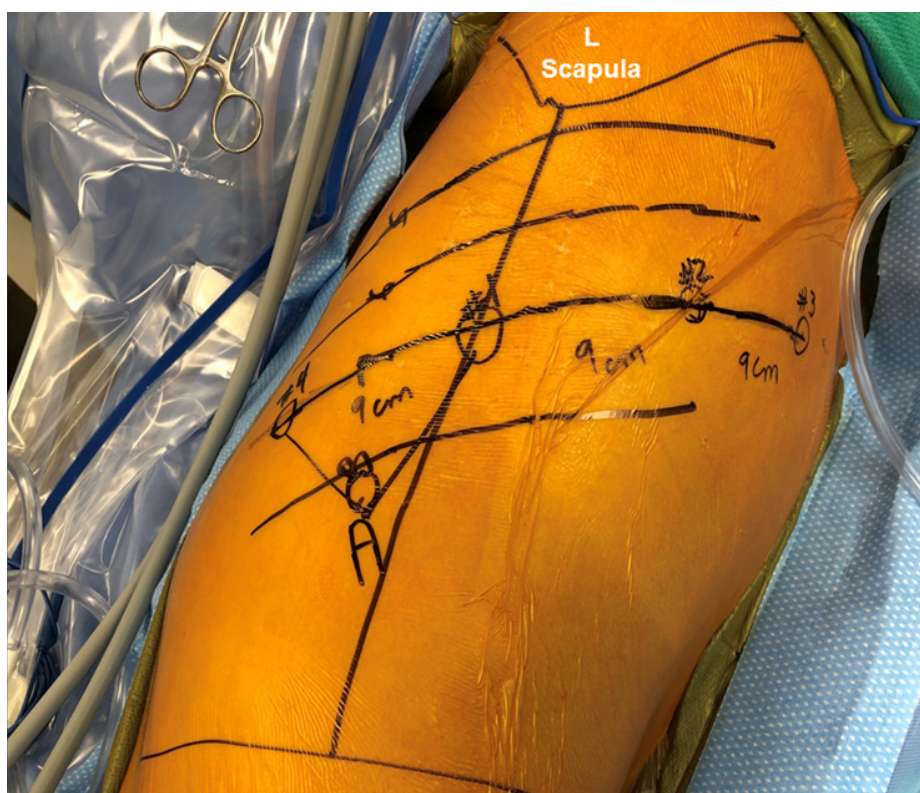


Figure 2. Port placement for robotic segmentectomy in the left chest (please see description in the text)

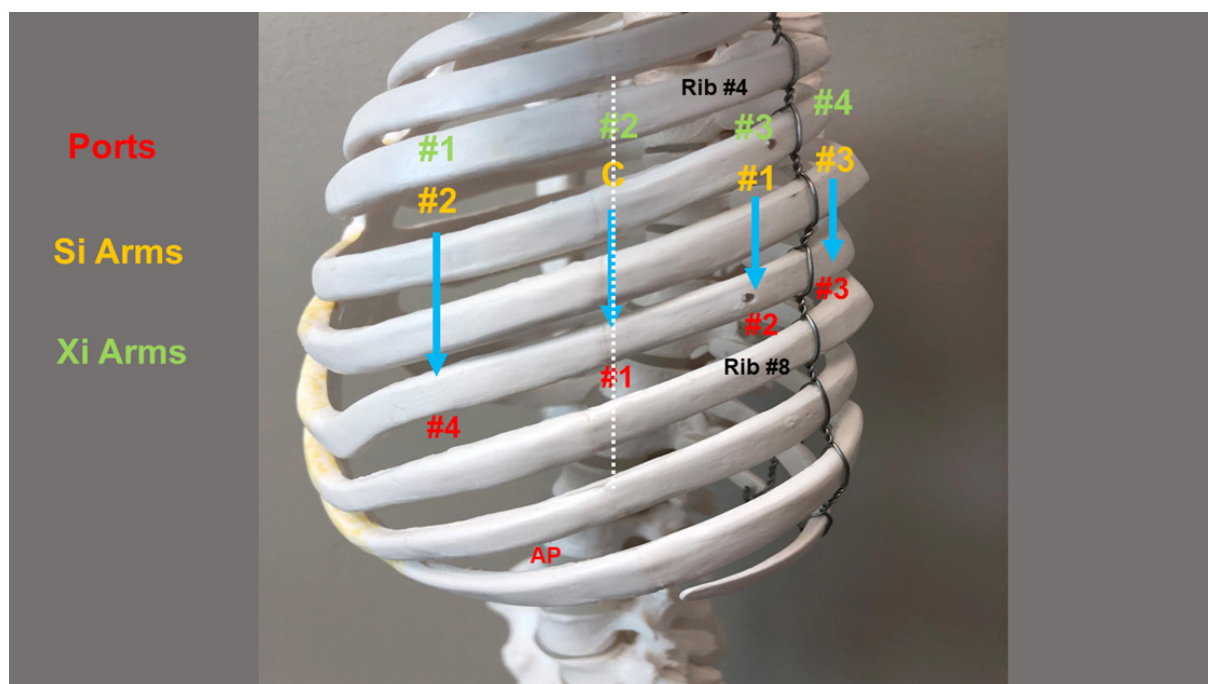


Figure 3. Port placement for robotic segmentectomy in the left chest. Dotted line: Scapular line; Red: Ports; Yellow: Si arm numbering; Green: Xi arm numbering; AP: assistant port

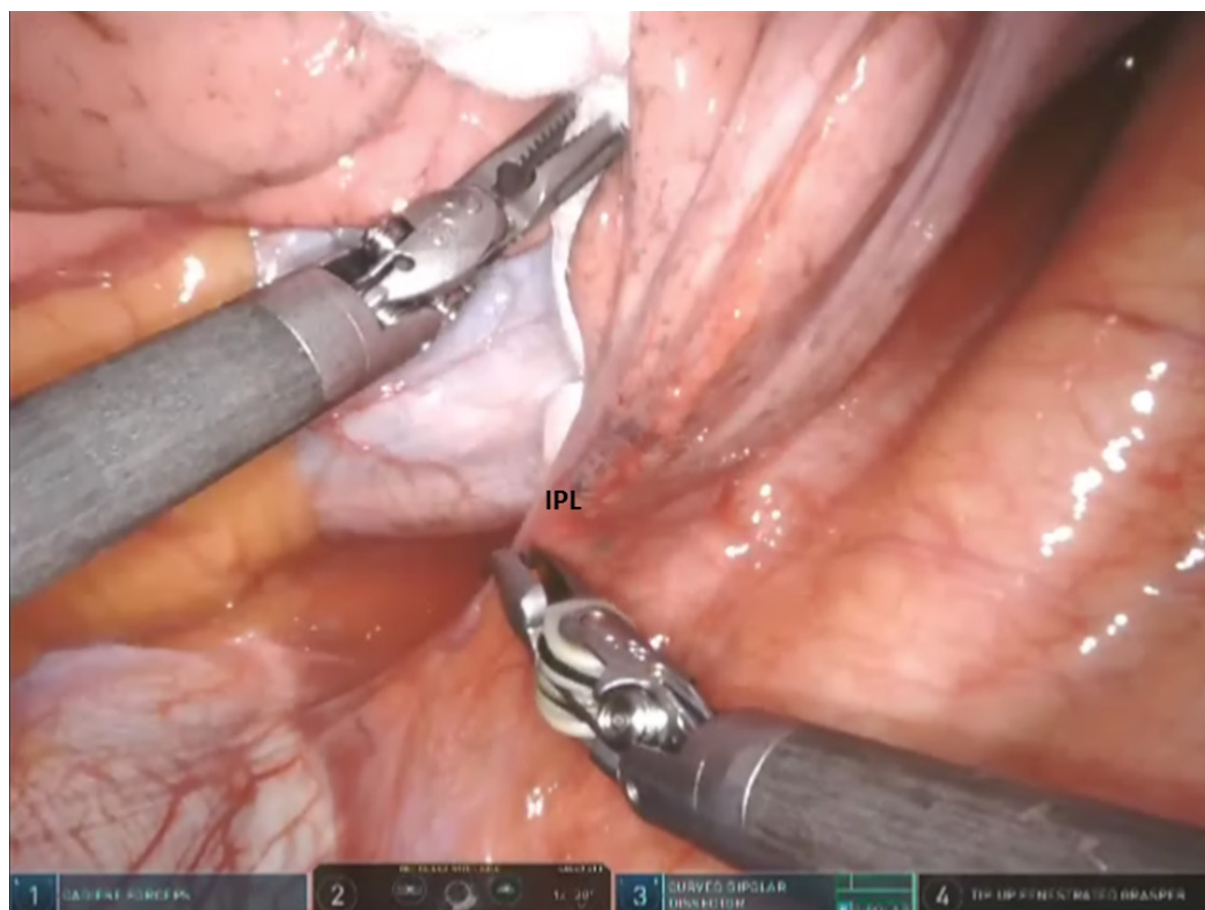


Figure 4. Left sided Segmentectomy: begin by dividing the IPL. IPL: inferior pulmonary ligament

scapular line. The Assistant Port #5 uses a 10-12 Versiport trocar and is placed in the 9th intercostal space and is triangulated between Port #1 and #4.

For the da Vinci Si robot, the bed is angled posteriorly away from the anesthesia machine and the robot is brought in over the head of the patient. For the Xi system, the robot is brought in from the back and perpendicular to the patient and the boom is rotated to the proper position.

One of the advantages of the Xi robot is that the surgeon can control the stapling device. We prefer a 30 mm stapler with a white load for the vascular structures, and a blue or green load for the bronchus and the lung tissue as judged by the size and thickness of the structure.

Instruments: 0° and/or 30° down viewing endoscope, 5 mm Thoracic Grasper, Cadere Forceps, and Curved Bipolar Dissector.

For all segmentectomies, begin by dividing the inferior pulmonary ligament and remove station #9, and station #8 [Figures 4 and 5]. The lung is retracted medially and anteriorly in order to remove lymph nodes from station #7. We find that pulling the nasogastric tube back above the area of subcarinal dissections opens the mediastinal space and facilitates the subcarinal and mediastinal dissection. After the mediastinal dissection, the nasogastric tube is advanced back into the stomach, placed on suction, and used to decompress the stomach and prevent gastric distension and the resultant elevation of the left hemidiaphragm. Next, open the pleura anterior to the vagus nerve. Identify the left mainstem bronchus

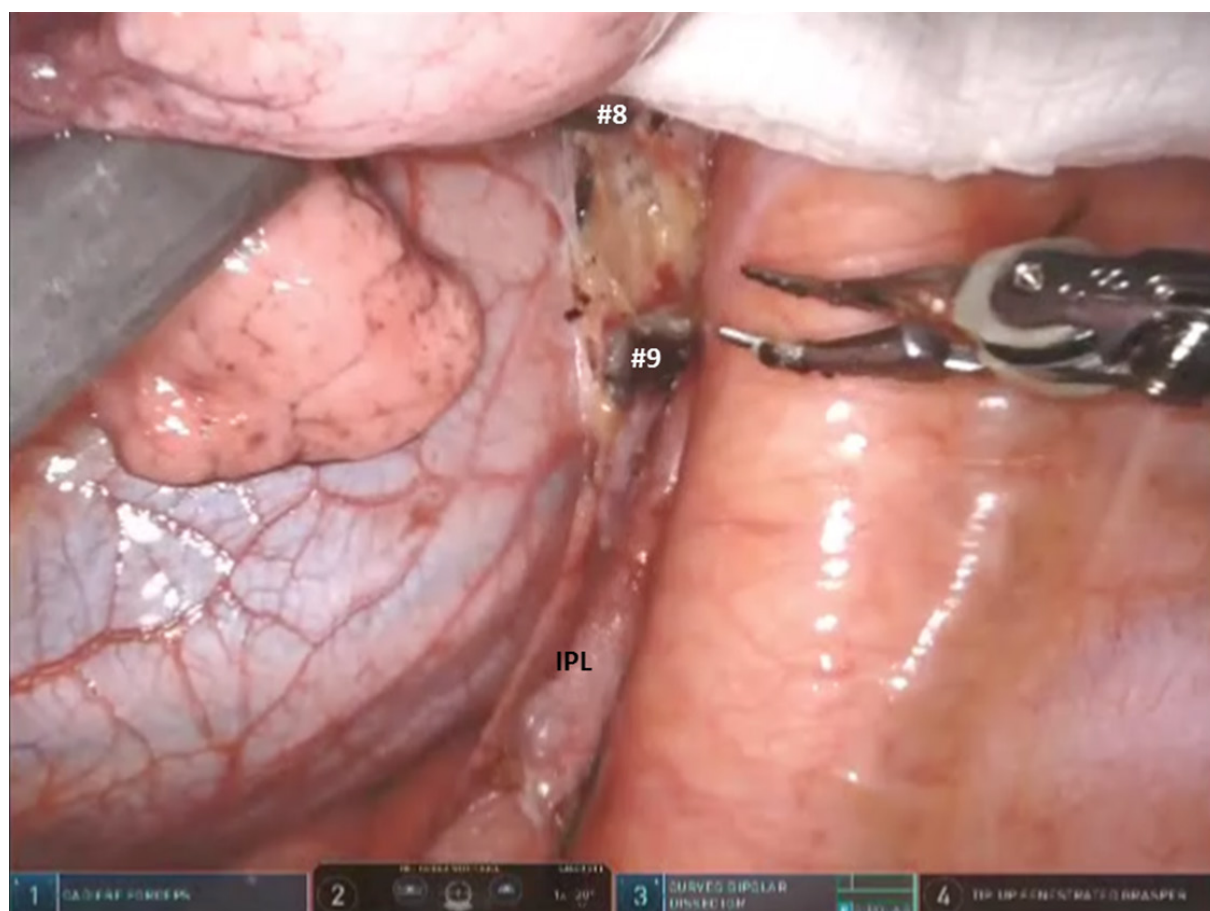


Figure 5. Left sided Segmentectomy: dissection and removal of station #9 and station #8 lymph nodes. IPL: inferior pulmonary ligament

and stay inferior to the edge of the cartilage. The station #7 nodal bundle is accessed between the inferior pulmonary vein and the left mainstem bronchus. The nodal bundle is traced to the carina and is then removed [Figure 6]. Next, the lung is retracted inferiorly, and pleura overlying the station #5 nodal bundle is opened. Station #5 nodes are removed [Figure 7].

The left main pulmonary artery is identified above the left main bronchus. The space between the pulmonary artery and the bronchus is opened and station #10L nodal bundle is identified overlying the superior border of the bronchus [Figure 8]. The space between the pulmonary artery and the aorta is cleared in order to visualize the nodal bundle which encases the apicoposterior trunk of the artery [Figure 9]. Care is taken to identify and preserve the vagus nerve and the recurrent laryngeal branch. After exposing the apicoposterior trunk, the station #10 nodal bundle is swept in an inferomedial direction, thereby exposing the underside of the truncus branch and its takeoff from the main pulmonary artery.

Next the upper and lower lobe are retracted in opposite directions and the fissure is identified. Dissection of nodal bundle in station #11 allows for the identification of the pulmonary artery in the fissure [Figure 10]. The artery is most superficial at the junction of the Lingula, upper lobe and the lower lobe. The subadventitial plane is entered, and dissection is carried posteriorly, under the pulmonary parenchyma in the posterior aspect of the fissure toward the main pulmonary artery. The Cadieere forceps is used to pass a vessel loop under the pulmonary parenchyma in the posterior aspect of the fissure. A stapler with a blue cartridge is used to divide the tissue in the posterior aspect of the fissure [Figure 11].

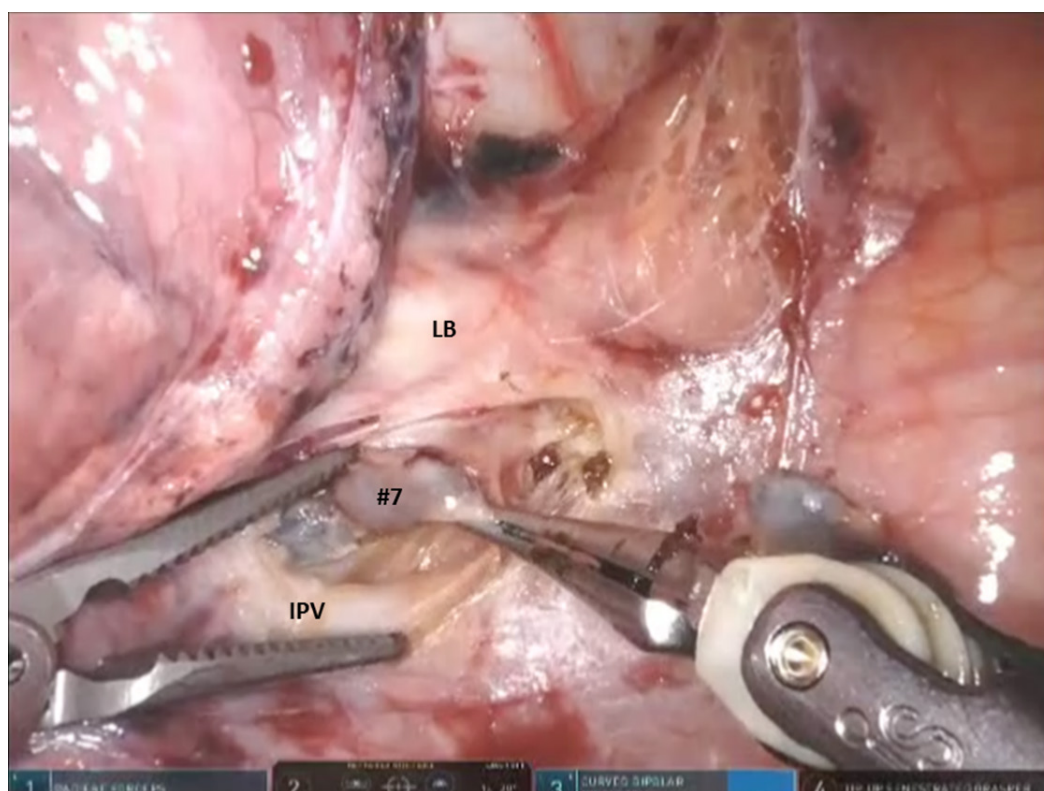


Figure 6. Left sided Segmentectomy: the station #7 nodal bundle is accessed between the IPV and the LB. IPV: inferior pulmonary vein; LB: left mainstem bronchus

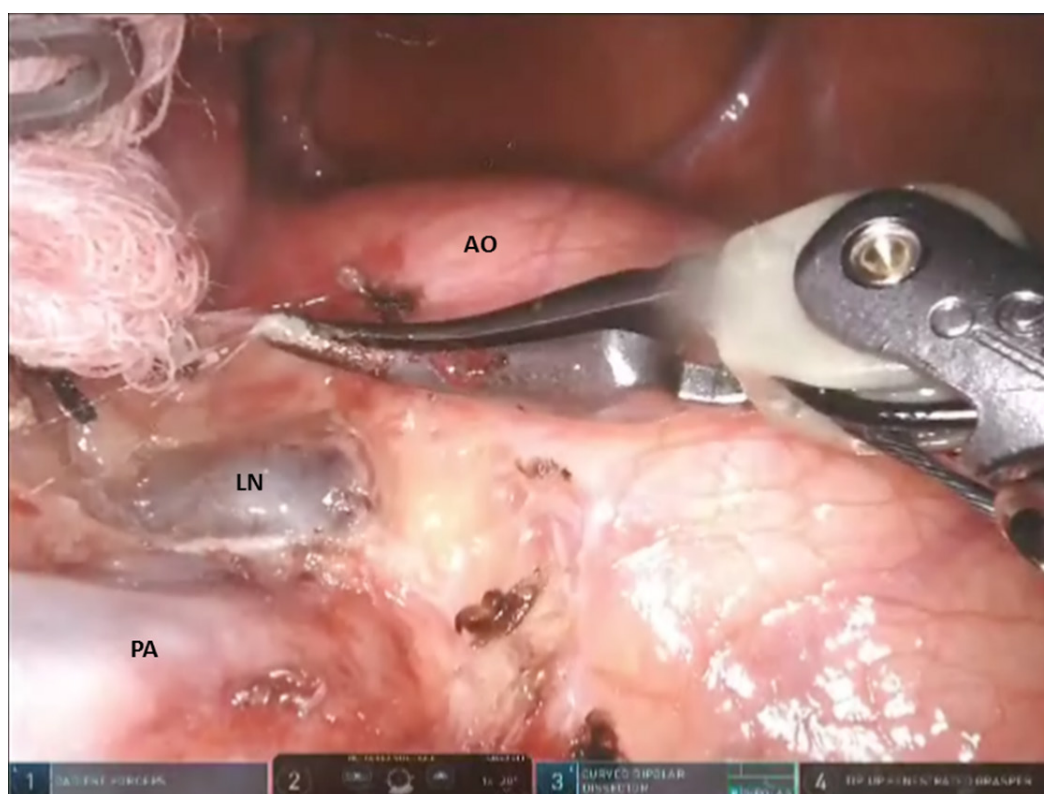


Figure 7. Left sided Segmentectomy: station #5L nodes are removed from the aorto-pulmonary window. AO: aorta; PA: pulmonary artery; LN: lymph node

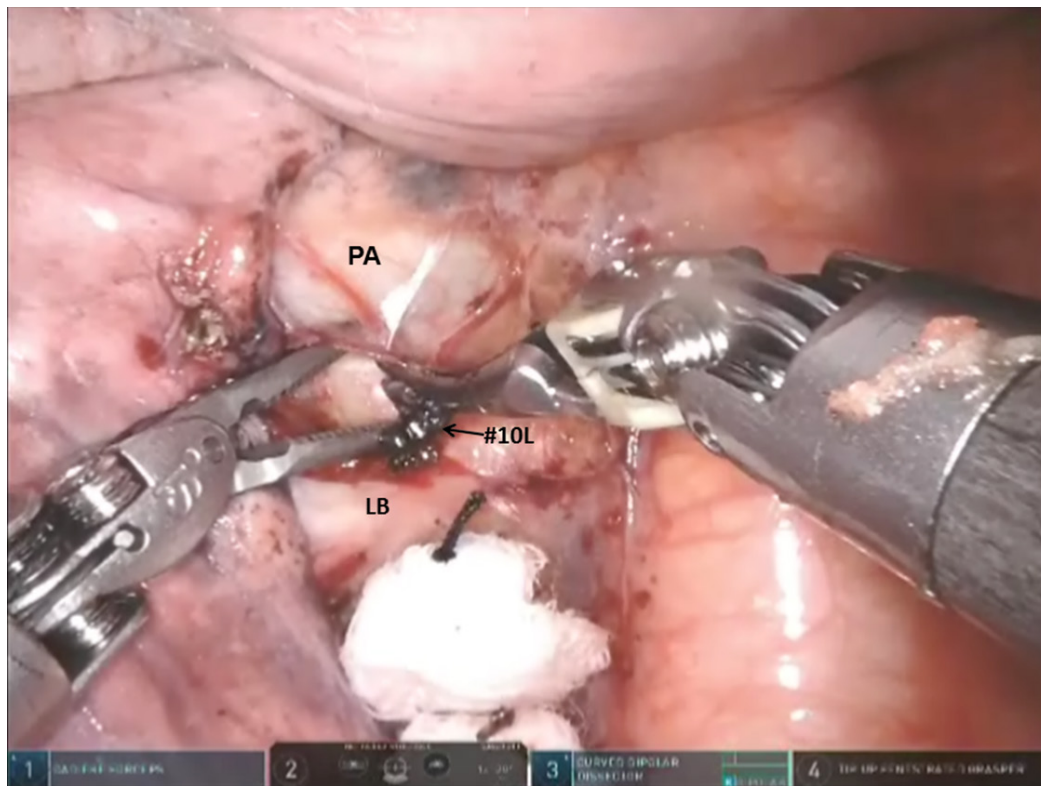


Figure 8. Left sided Segmentectomy: the space between the PA and the LB is opened and the station #10L nodal bundle is identified overlying the superior border of the bronchus. PA: pulmonary artery; LB: left mainstem bronchus

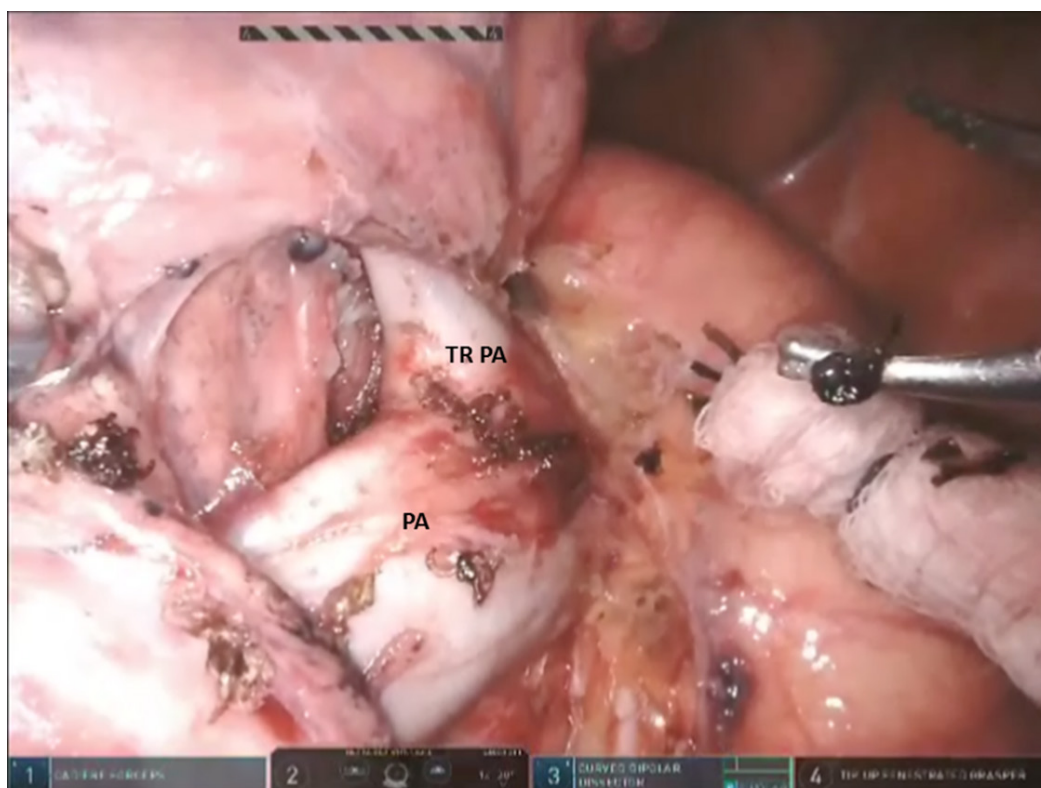


Figure 9. Left sided Segmentectomy: clear the nodal bundle which encases the apicoposterior trunk (TRPA) of the left PA. TRPA: truncus branch of pulmonary artery; PA: pulmonary artery

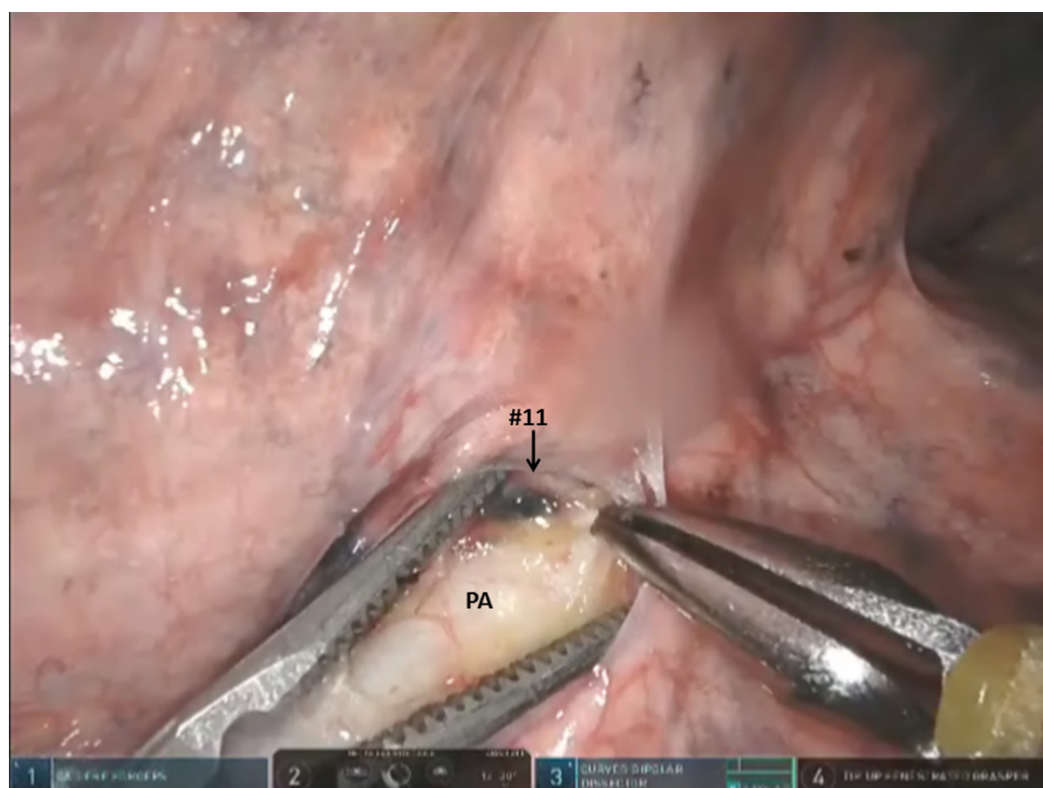


Figure 10. Left sided Segmentectomy: dissection of nodal bundle in station #11 allows for the identification of the PA in the fissure. PA: pulmonary artery

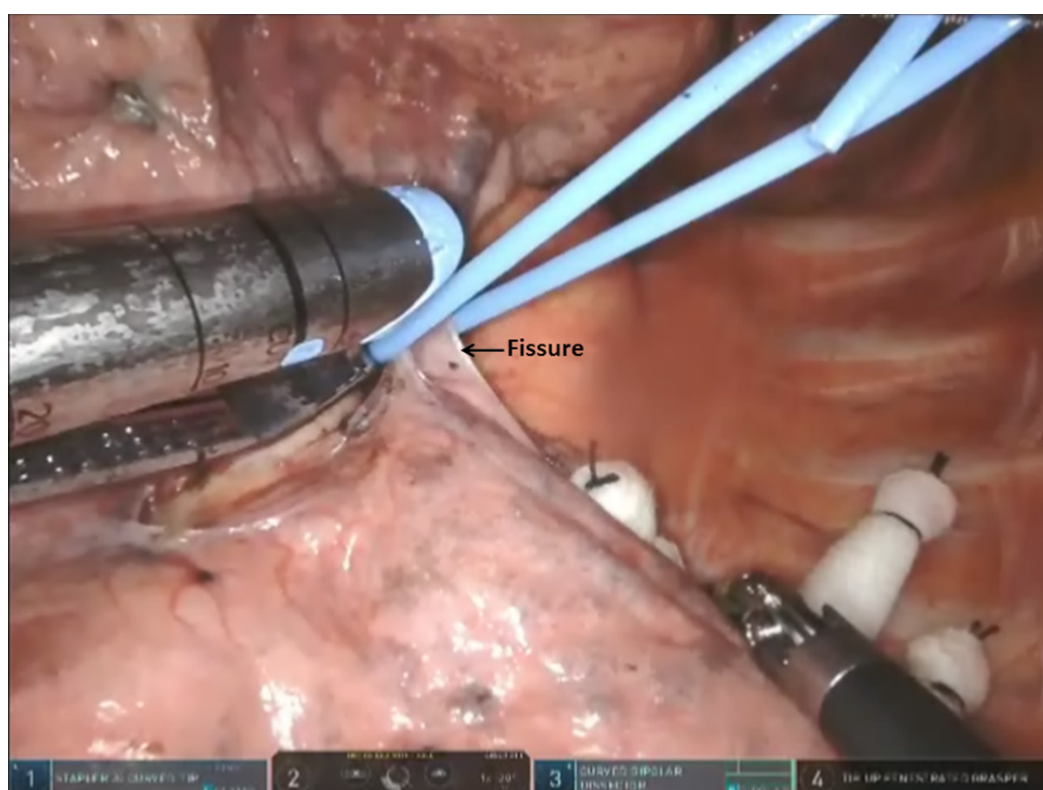


Figure 11. Left sided Segmentectomy: pass a vessel loop under the pulmonary parenchyma in the posterior aspect of the fissure

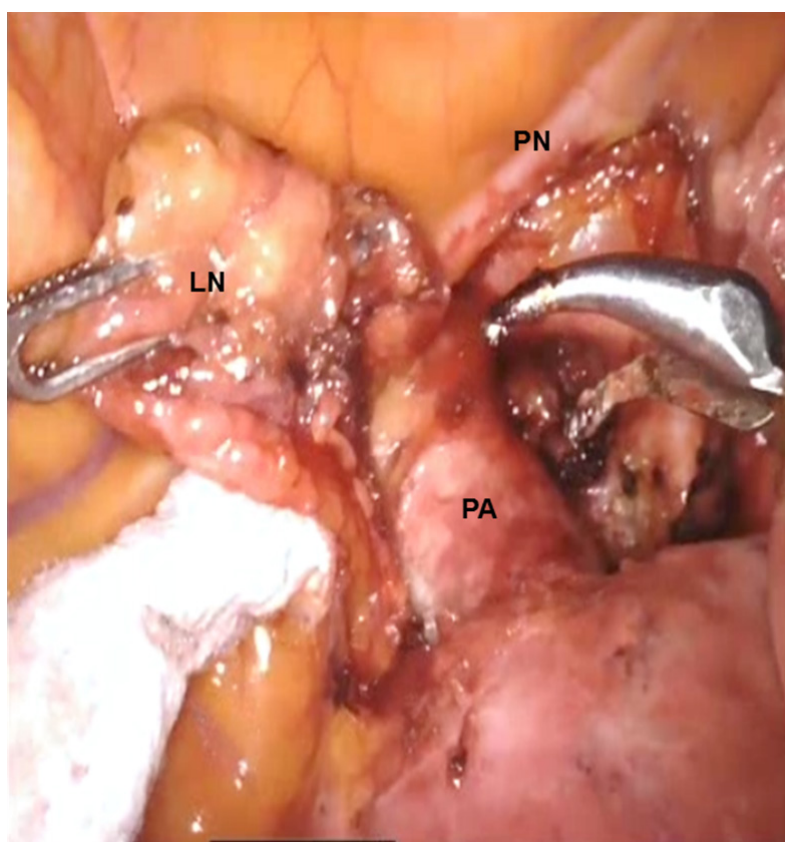


Figure 12. LS3 Segmentectomy: the nodes in station #5 (LN) are removed and the proximal left PA is exposed just posterior to the left PN. PA: pulmonary artery; PN: phrenic nerve; LN: lymph node

Left upper lobe anterior anatomic segmentectomy (S3)

Following the dissection of mediastinal nodes, the lung is retracted posteriorly and the anterior hilum is approached. The nodes in station #5 are removed and the proximal left pulmonary artery is exposed just posterior to the left phrenic nerve [Figure 12]. The nodes between the superior pulmonary vein and the pulmonary artery are dissected and removed. The superior pulmonary vein is separated from the underlying pulmonary artery [Figure 13]. Figure 14 shows the anatomic relationship among the vein, artery, and bronchus in segment S3 (V3, A3 and B3).

V3 is encircled, elevated with a vessel loop, and divided with a stapler with a white cartridge. Care is taken to preserve the V1 branch to the S1 segment of the upper lobe. The B3 bronchus is encircled, elevated off the pulmonary artery, and divided with a stapler using a purple cartridge. Division of the B3 facilitates division of the A3 PA branch(es). The A3 PA branch is encircled with a vessel loop and divided with a stapling device. The A3 PA branches can be divided before dividing B3; however, this usually requires suture ligation and division of the A3. Next the intersegmental fissures between S1 + S2 and S3 and between S4 + S5 and S3 are delineated either using indocyanine green if using the Xi robot or inflation technique and divided using a stapler carrying a green cartridge [Figure 15].

Left upper lobe apical and posterior anatomic segmentectomy (S1 + S2)

The approach to these left sided segments is similar. Although individual posterior (S2) segmentectomy is possible, instead of an individual apical segmentectomy, many times an apicoposterior (S1 + S2) segmentectomy is performed on the left side.

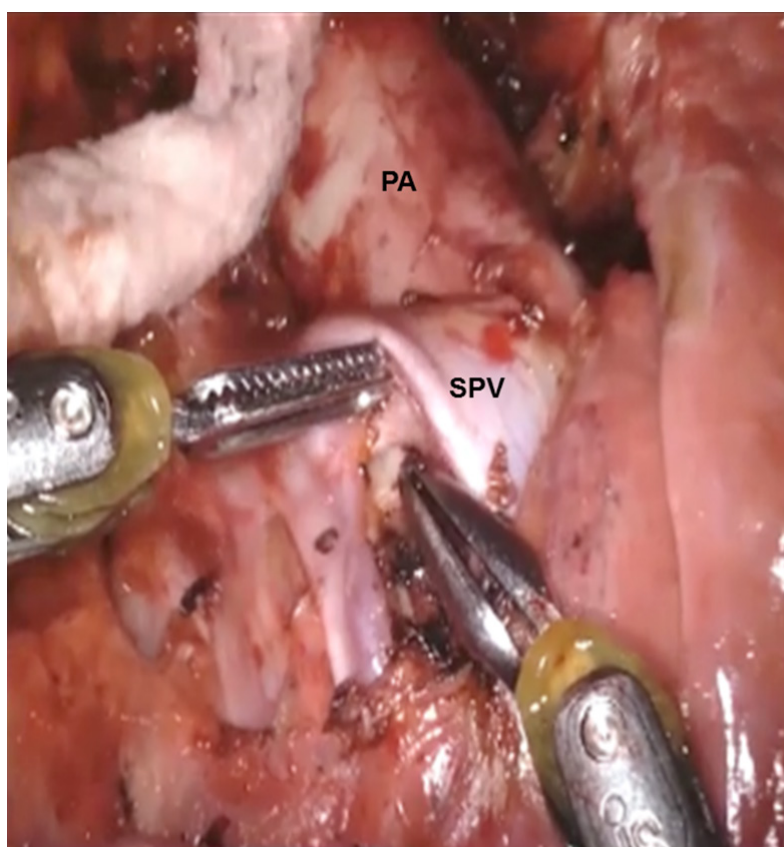


Figure 13. LS3 Segmentectomy: the nodes between the SPV and the PA are dissected and removed. PA: pulmonary artery; SPV: superior pulmonary vein

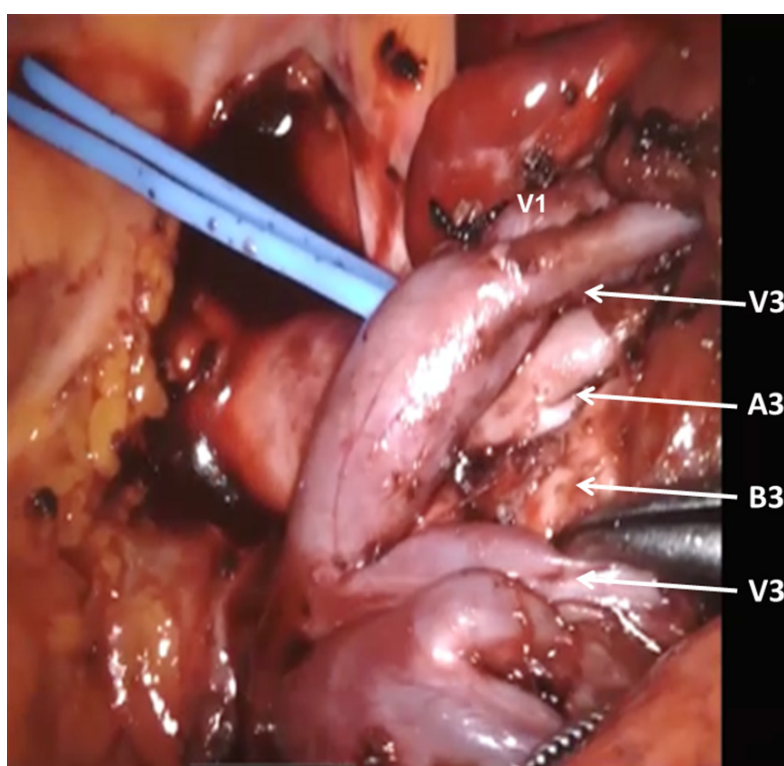


Figure 14. LS3 Segmentectomy: the anatomic relationship between S3 segmental veins (V3), S3 segmental artery (A3), and S3 segmental bronchus (B3)

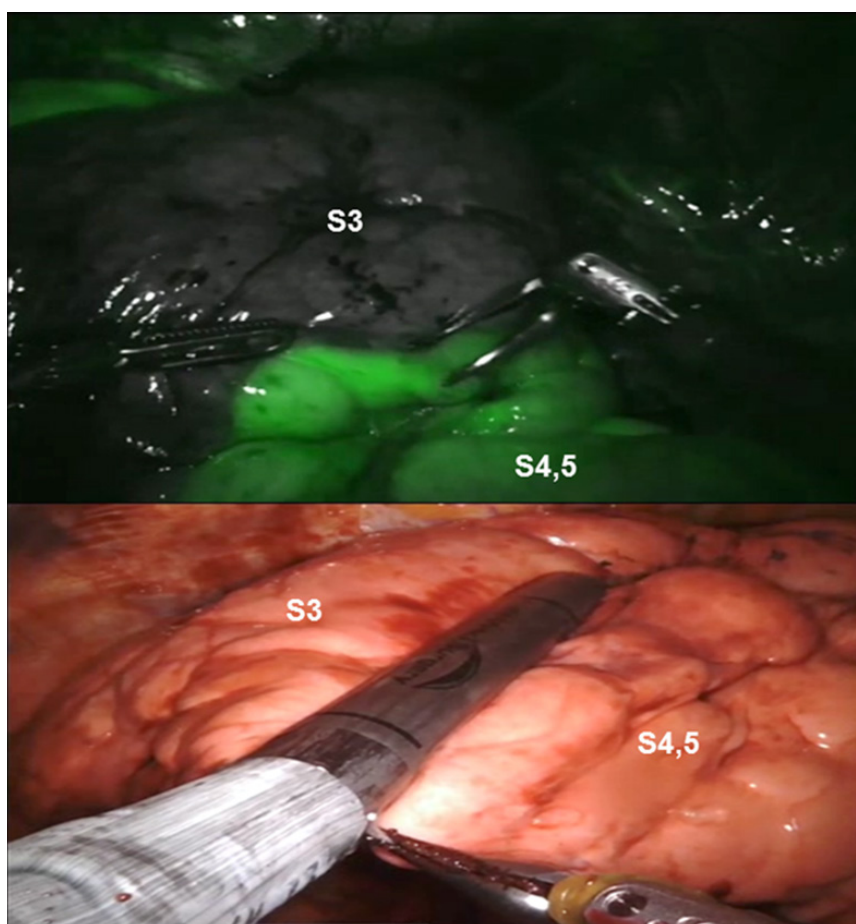


Figure 15. LS3 Segmentectomy: the intersegmental fissure between S3, and S4, 5 is delineated either by using Indocyanine Green if using the Xi robot or by inflation if using the Si robot

As with all segmentectomies, the procedure begins with mediastinal nodal dissection as has been described previously.

For a posterior S2 or apicoposterior S1 + S2 segmentectomy, the pulmonary artery branches to the respective segments as identified in [Figure 16](#). The branches are encircled, elevated with a vessel loop, and divided with a vascular stapler carrying a white load. Following the division of the pulmonary artery branches, the bronchus is approached from the back. The segmental bronchus is isolated, the N1 nodes are excised, and the bronchus is encircled and divided with a stapler with a purple or blue cartridge [\[Figure 17\]](#). For these segments, the segmental veins are usually taken with division of the fissure. The intersegmental fissure is identified as has been outlined previously and divided in a stepwise progressive manner using a stapling device with a green cartridge [\[Figure 18\]](#).

Left upper lobe lingulectomy and anatomic segmentectomy (S4 + S5)

Lingulectomy can be performed with either a vein first or artery first technique. The advantage of the artery first technique is that the fissure is approached first, station #11 nodes are removed first, and if they are positive, a left upper lobectomy is performed.

After a complete mediastinal nodal dissection as with the other left sided segmentectomies, the oblique fissure is opened and the subadventitial plane above the descending pulmonary artery is entered [\[Figure 19\]](#). The “V” shaped space between the lower lobe pulmonary artery and the Lingular artery is dissected and all N1 nodes are removed.

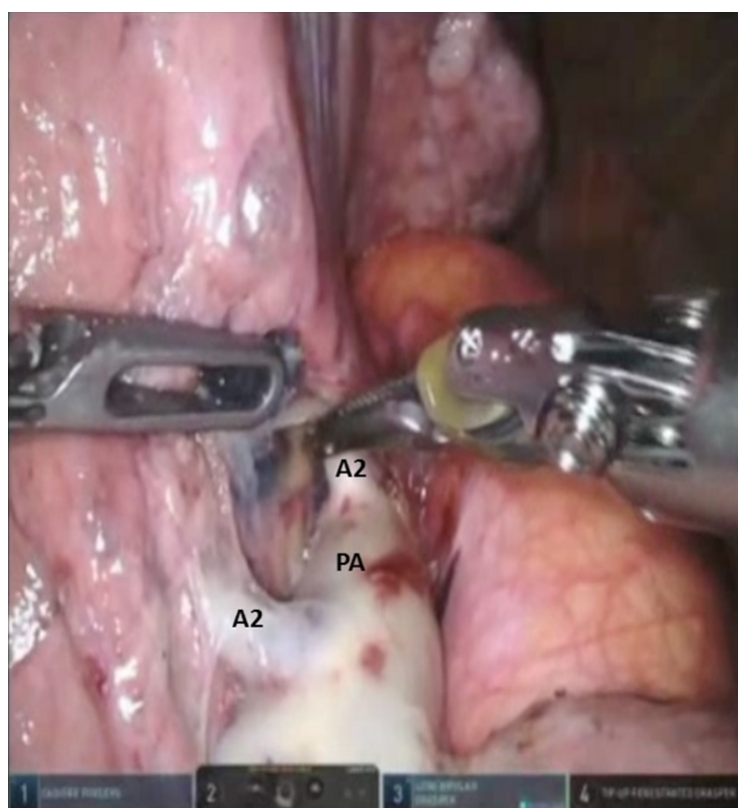


Figure 16. LS1, S2 Segmentectomy: the pulmonary artery branch to the posterior segment (A2) are identified. PA: pulmonary artery



Figure 17. LS1, S2 Segmentectomy: the segmental bronchus (B) is isolated and divided

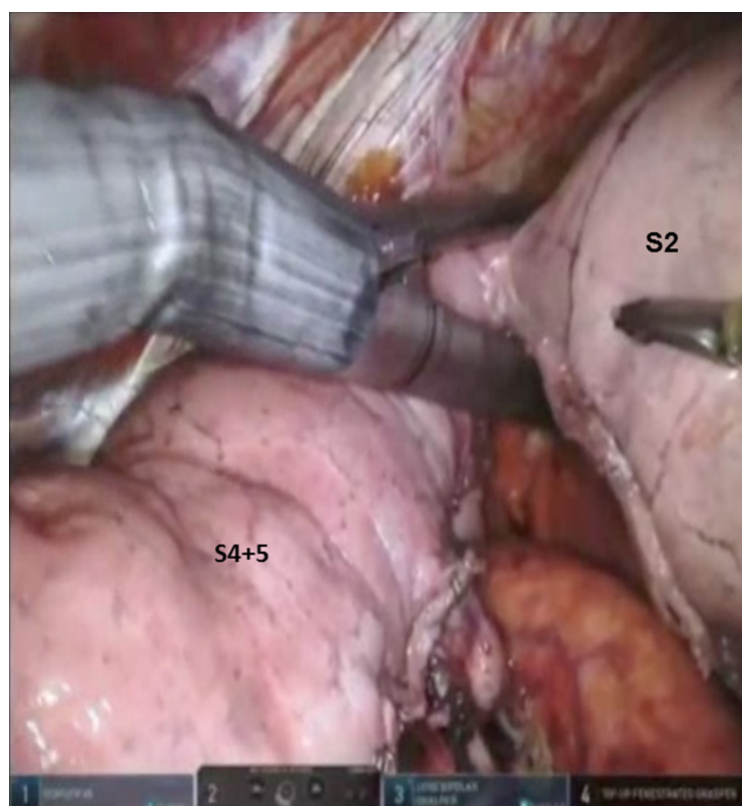


Figure 18. LS1, S2 Segmentectomy: the intersegmental fissure between S1 + S2 and S4 + S5 segments is divided in a stepwise progressive manner using a stapling device with a Green load

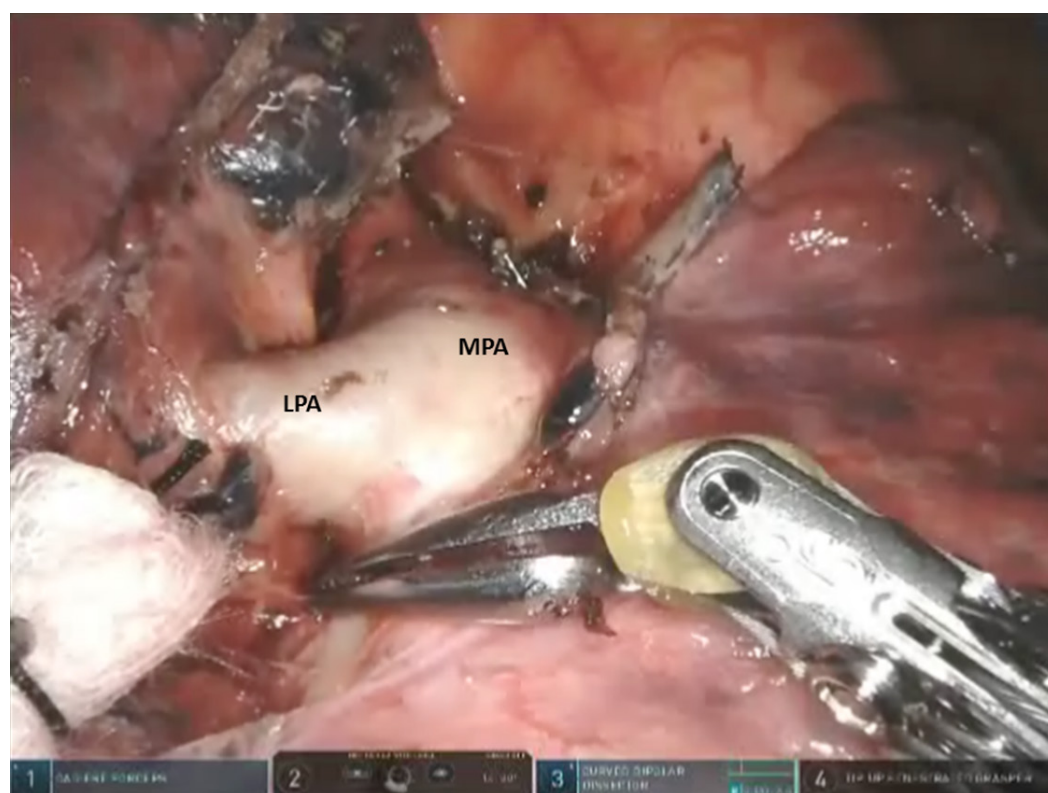


Figure 19. Lingulectomy (LS4, LS5): the oblique fissure is opened and the subadventitial plane above the descending pulmonary artery is entered. MPA: main pulmonary artery; LPA: lingular pulmonary artery

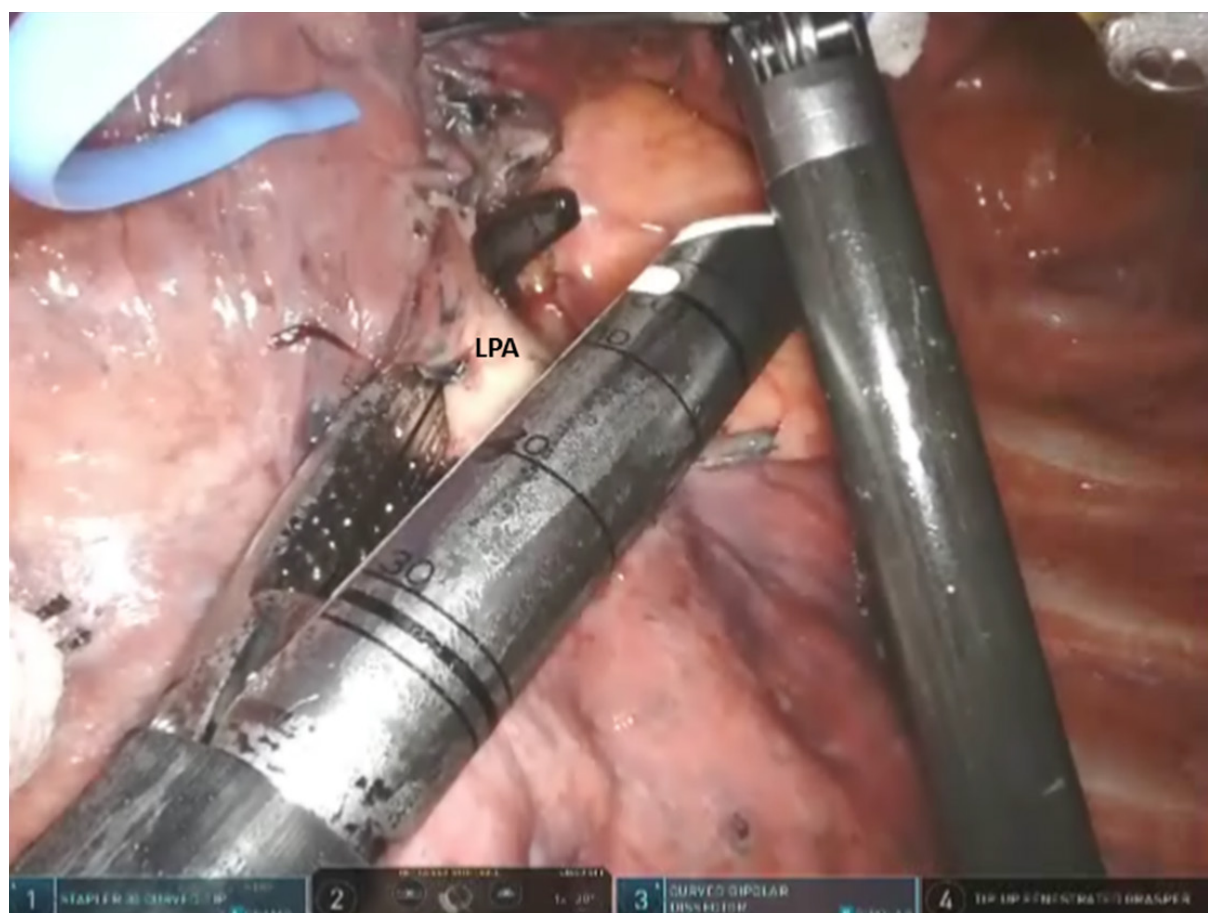


Figure 20. Lingulectomy (LS4, LS5): LPA is encircled and elevated with a vessel loop and divided with a stapler carrying a white cartridge. LPA: lingular pulmonary artery

Next, the lung is retracted posteriorly, and the anterior hilum is approached. The space between the superior and inferior pulmonary veins is developed and the nodes are removed. The superior pulmonary vein is dissected away from the underlying pulmonary artery, encircled with a vessel loop, and elevated. After the entire superior pulmonary vein is dissected, the Lingular vein(s) are identified, encircled, elevated with a vessel loop, and divided with a vascular stapler. Then, the anterior aspect of the oblique fissure is divided by passing a stapler with a blue cartridge from an anterior to posterior direction, heading toward the space between the Lingular artery and the inferior pulmonary artery. This enables easy access to the Lingular pulmonary artery which is encircled, elevated with a vessel loop, and divided with a stapler carrying a white cartridge [Figure 20]. Division of the fissure also enables access to the Lingular bronchus. The Lingular bronchus is encircled and elevated with a vessel loop; the anesthesiologist removes any indwelling suction catheters and the bronchus is divided with a stapler using a green cartridge [Figure 21]. Finally, using the techniques which have been outlined earlier, the intersegmental fissure between S1 + S2, S3, and the Lingula are identified [Figure 22]. The lung parenchyma is then divided with multiple firings of a stapling device with a blue or green cartridge.

Robotic left lower lobe anatomic superior segmentectomy (S6)

Port placement and instruments are similar to the left upper lobe segmentectomy procedures.

Following the complete mediastinal dissection which has been outlined previously, the pulmonary artery is identified in the oblique fissure. The subadventitial plane overlying the pulmonary artery is entered, and

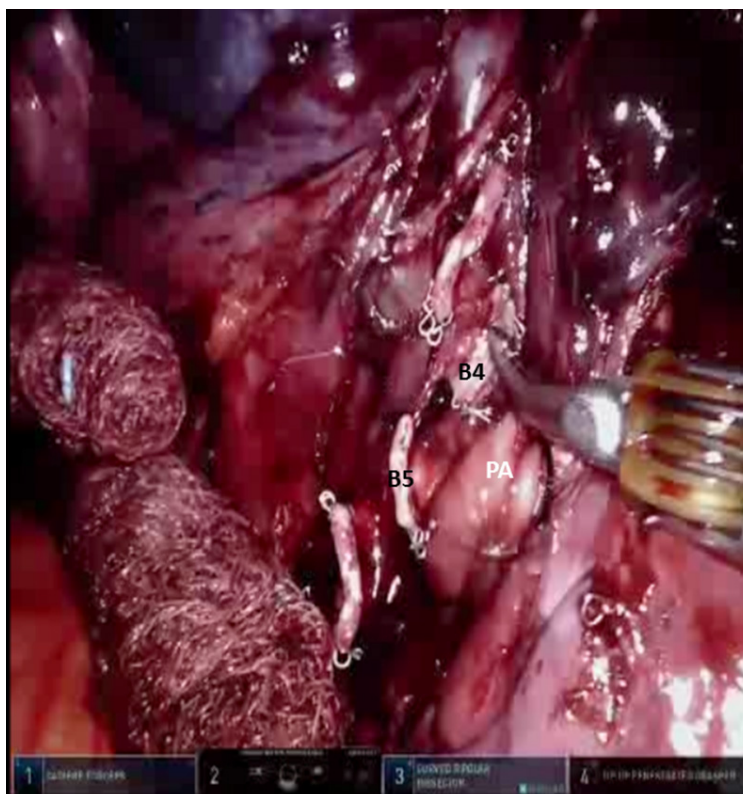


Figure 21. Lingulectomy (LS4, LS5): the stump of the Lingular bronchus is seen (B4, B5). PA: main pulmonary artery



Figure 22. Lingulectomy (LS4, LS5): the intersegmental fissure between S2 and the Lingula is identified using ICG dye. ICG: indocyanine green

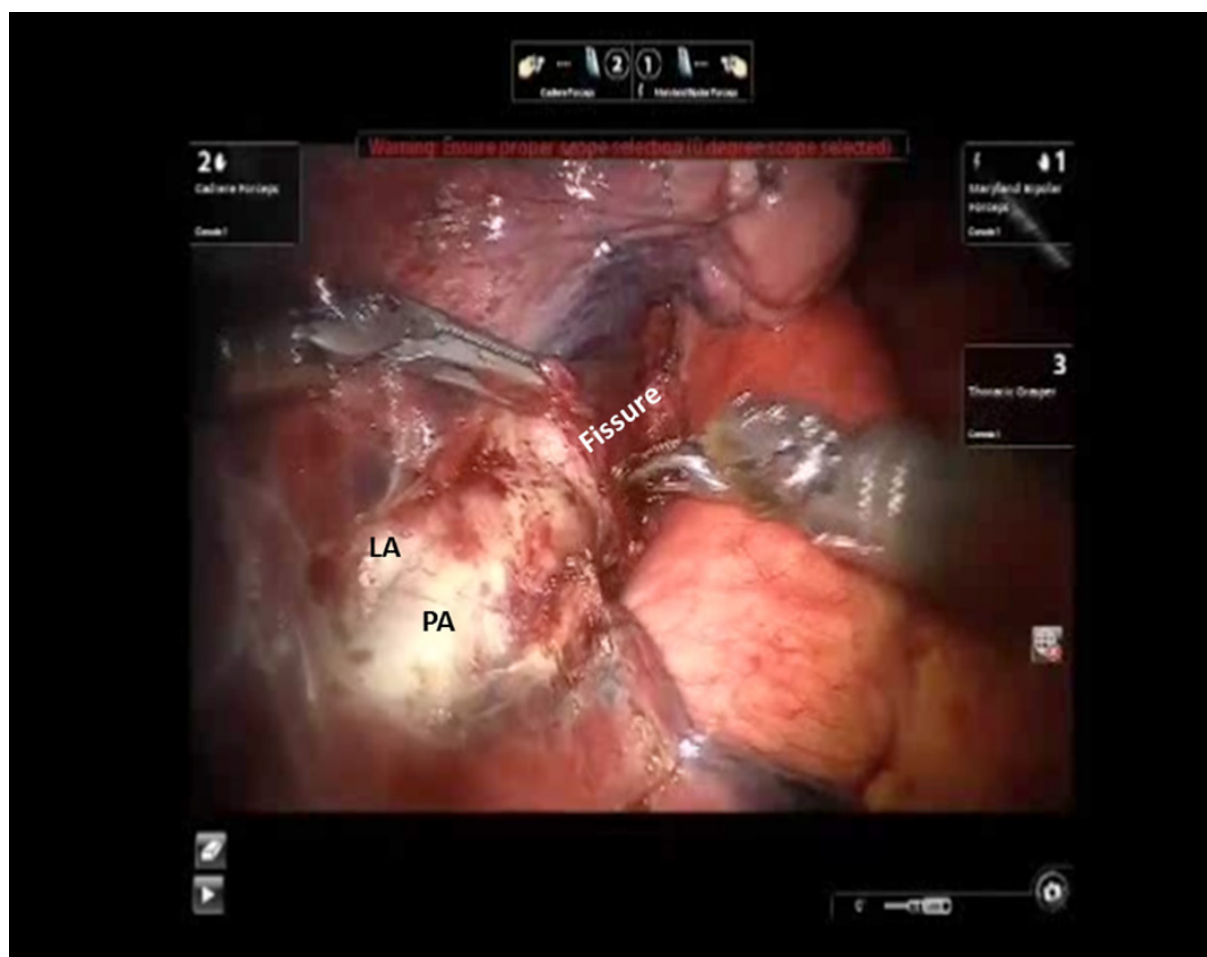


Figure 23. LS6 Segmentectomy: the subadventitial plane is entered, and dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure toward the main pulmonary artery. LA: lingular artery; PA: descending main pulmonary artery

dissection is carried posteriorly under the pulmonary parenchyma in the posterior aspect of the fissure toward the main pulmonary artery [Figure 23]. A pair of Cadiere forceps is used to pass a vessel loop under the pulmonary parenchyma in the posterior aspect of the fissure. A stapler with a blue cartridge is then used to divide the tissue in the posterior aspect of the fissure. The subadventitial plane is then developed anteriorly in order to identify the descending branch of the pulmonary artery. The anterior aspect of the oblique fissure is divided. The superior segmental pulmonary artery is identified. The Cadiere forceps is passed under the superior segmental pulmonary artery, a vessel loop is passed underneath and used to encircle and elevate the vessel, and the vessel is divided with a stapler with a white vascular cartridge introduced from a medial to lateral direction [Figure 24].

The lung is elevated and retracted medially. The Cadiere forceps is passed from a medial to lateral direction under the inferior pulmonary vein and a vessel loop is used to encircle and elevate the vein [Figure 25]. The superior segmental vein is identified, encircled, and divided using a stapler with a white vascular cartridge introduced from inferior to superior direction [Figure 26]. The nodes overlying the left lower lobe bronchus are swept toward the specimen. The B6 bronchus is identified, encircled, and divided [Figure 27]. The intersegmental fissure between the S6 and the basal segments of the lower lobe is identified as has been outlined previously and divided using a stapling device.

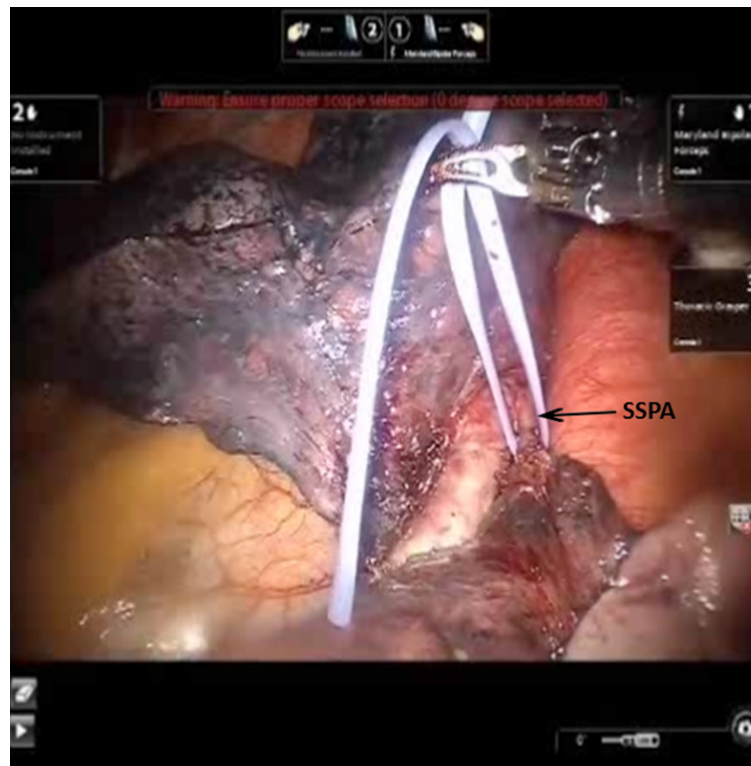


Figure 24. LS6 Segmentectomy: a vessel loop is passed underneath SSPA and used to encircle and elevate the vessel. SSPA: superior segmental pulmonary artery



Figure 25. LS7-LS10 Segmentectomy: the IPV is isolated. LMB: left mainstem bronchus; IPV: inferior pulmonary vein

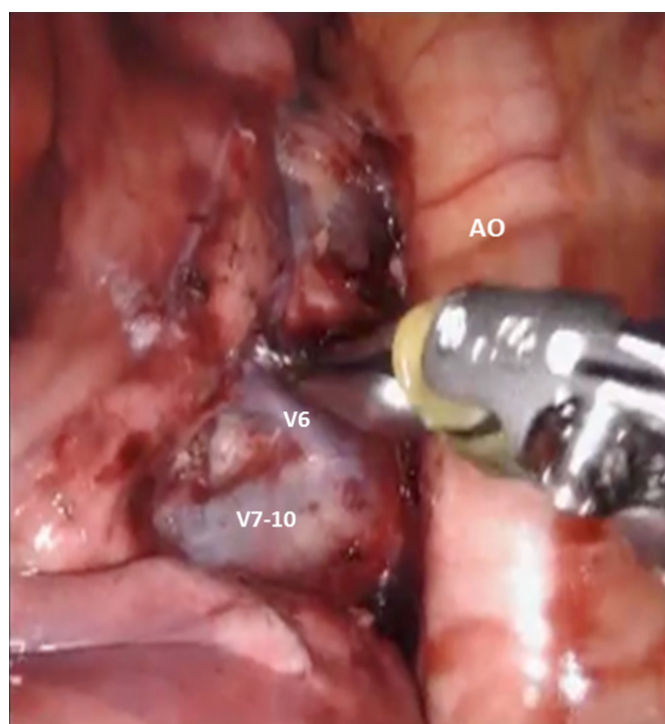


Figure 26. LS7-LS10 Segmentectomy: isolation of the left lower lobe basal vein (V7-10) from superior segmental vein (V6). AO: aorta

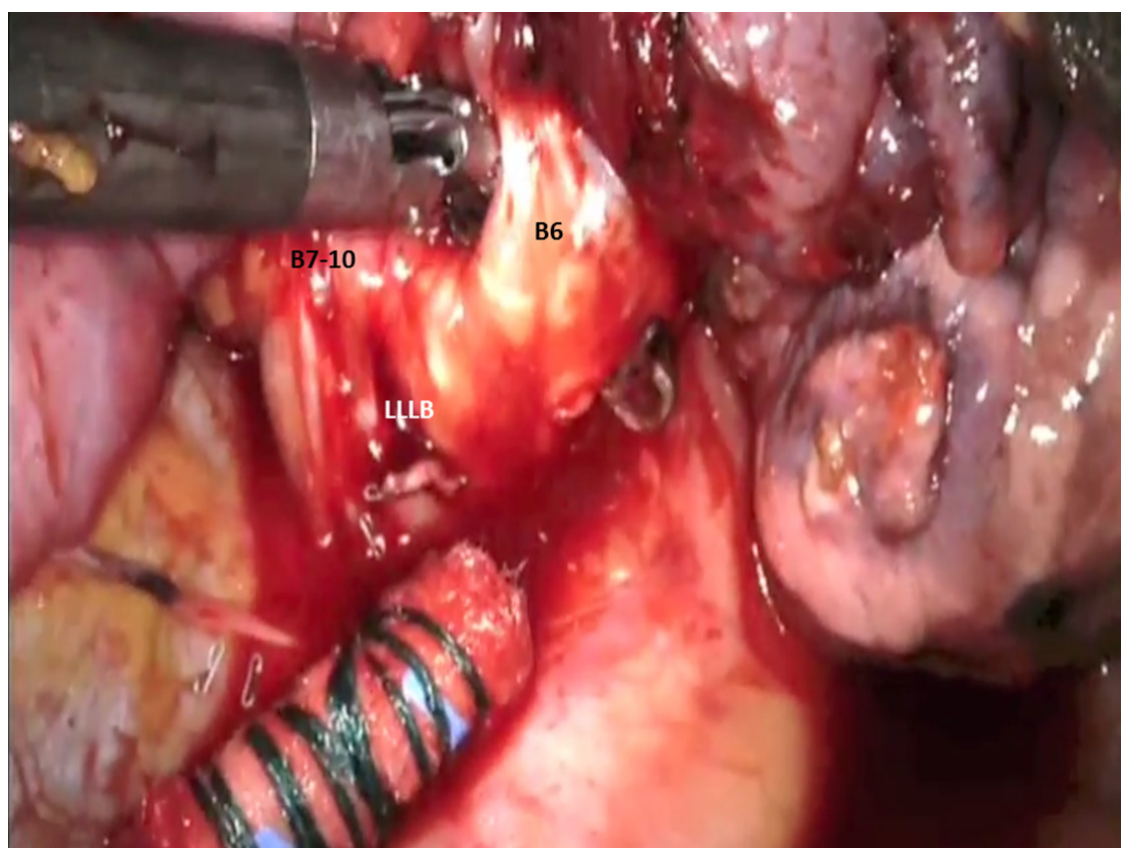


Figure 27. LS6 Segmentectomy: B6 bronchus is identified, encircled, and divided. LLLB: left lower lobe bronchus; B7-10: bronchus to basal segment of left lower lobe

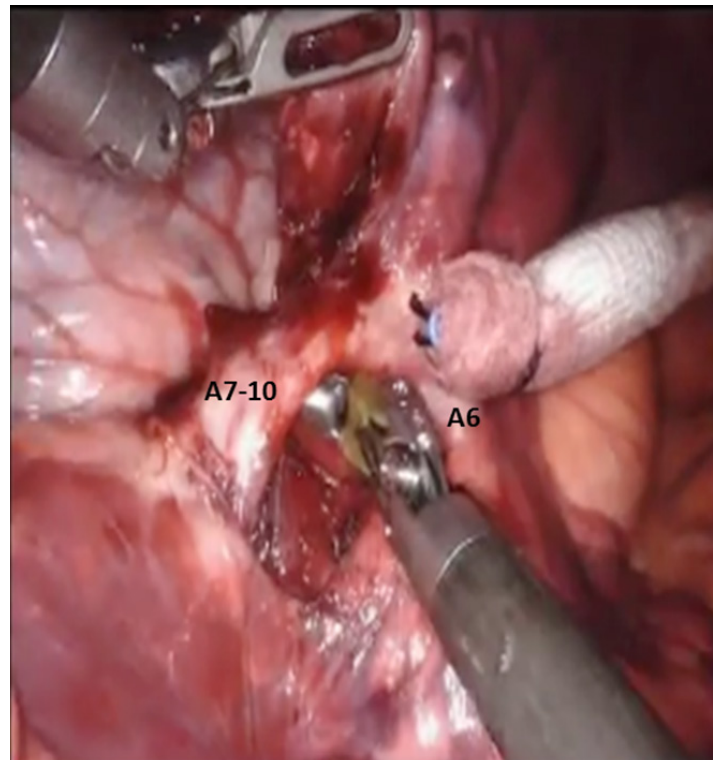


Figure 28. LS7-LS10 Segmentectomy: the basal branch of the left pulmonary (A7-10) is encircled and divided. A6: pulmonary artery to superior segment of left lower lobe (S6)

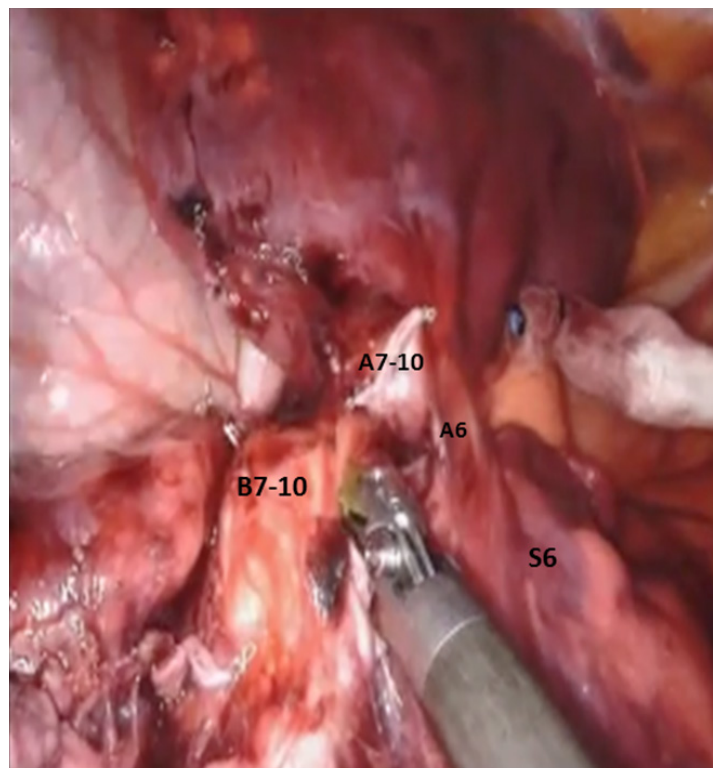


Figure 29. LS7-LS10 Segmentectomy: the bronchus to the basal segment (B7-10) is encircled and divided. A7-10: stump of the divided pulmonary artery branch to basal segment; A6: pulmonary artery branch to superior segment of left lower lobe (S6); S6: superior segment of left lower lobe

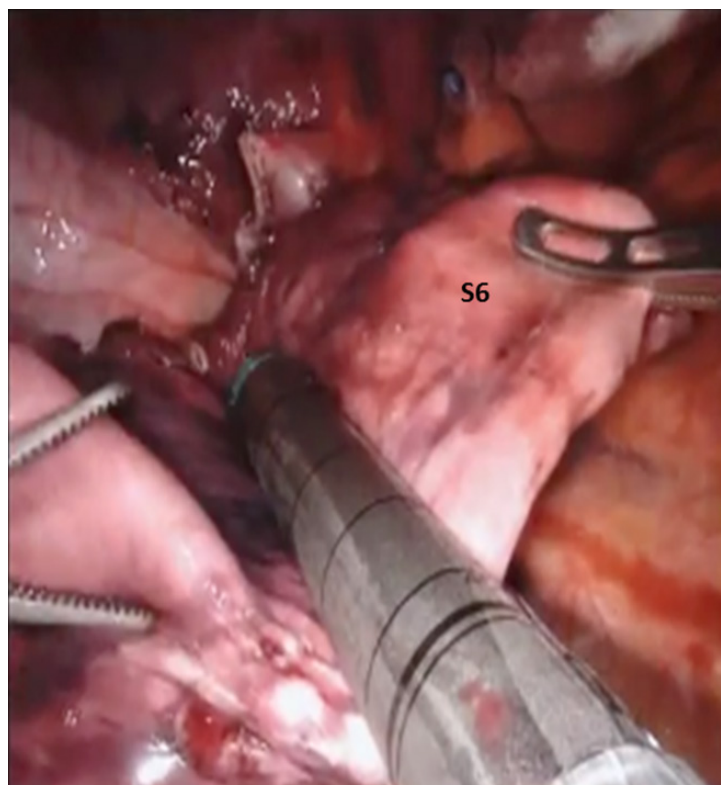


Figure 30. LS7-LS10 Segmentectomy: the intersegmental fissure is identified and divided using a stapler with a green cartridge

Robotic left lower lobe anatomic basal segmentectomy (S7-S10)

The approach to this segmentectomy is similar to superior segmentectomy (S6). Following the complete mediastinal nodal dissection, the inferior pulmonary vein is encircled with a vessel loop and elevated. Then the superior segmental vein is identified, thereby allowing for identification of the basal branch of the inferior pulmonary vein. The basal vein (V7-10) is then divided with a stapling device with a white cartridge. Next, the pulmonary artery is isolated in the fissure as has been described previously. The left lower lobe pulmonary artery is identified [Figure 28]. The basal branch of the left pulmonary artery is encircled and elevated with a vessel loop and divided with a vascular stapler. Following the division of the A7-10, the bronchus to the basal segment (B7-10) is encircled and divided with a stapler carrying a blue cartridge [Figure 29]. Finally the intersegmental fissure is identified and divided using a stapler with a green cartridge [Figure 30].

CONCLUSION

Anatomic pulmonary segmentectomy in patients with early stage lung cancer is an oncologically efficacious procedure. The surgical robot allows for precise dissection of the segmental bronchopulmonary structures while minimizing trauma to surrounding tissues, and it allows for thorough and complete dissection of the mediastinal nodes. Robotic segmentectomy should be considered when planning a lung sparing operation in patients with small tumors, in elderly patients or patients with borderline lung function.

DECLARATIONS

Authors' contributions

Contributed equally to the performance of the surgeries, collection of data and writing the manuscript: Gharagozloo F, Meyer M

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Not applicable.

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None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Robotic vs. laparoscopic major hepatectomy

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Abstract

The introduction of laparoscopic technology and surgical robots in hepatobiliary surgery in the 1990s and 2000s, respectively, has dramatically revolutionized the field. Even though laparoscopic and robotic major hepatectomy was slower to adopt compared to minimally-invasive minor hepatectomy, the number of major hepatectomies performed with both approaches worldwide has significantly increased and is still rising. Despite the few comparative studies between laparoscopic and robotic major hepatectomy, most studies are focused on describing the procedures or reporting the outcomes of each method, either separately, or mixed with minor hepatectomies. Based on the available data, the direct comparison between the two techniques has shown that when robotic major hepatectomy is performed by experienced hepatobiliary surgeons in high-volume centers, it can lead to similar operating times, estimated blood loss, hospital length of stay, complication and mortality rates compared to its laparoscopic counterpart. The likelihood of achieving a margin-negative resection in cancer patients, as well as long-term disease-free and overall-survival are comparable between the groups. However, broader adoption of the robotic approach might be a hurdle in low-volume centers due to the high fixed capital and annual maintenance cost of the surgical robot.

Keywords: Hepatectomy, liver resection, major hepatectomy, laparoscopic, robotic, minimally-invasive



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INTRODUCTION

The introduction of minimally-invasive technology in the approach of liver disorders in the early 1990s has since revolutionized the field of liver surgery^[1-3]. Laparoscopic liver surgery does not only include pure laparoscopy, but also hand-assisted laparoscopic, as well as hybrid approaches, where the initial part of the procedure (i.e., liver mobilization, early dissection) is done laparoscopically, while later a small incision is made to complete the transection of the liver parenchyma^[6,7]. The liver is classified in individual territories according to the segmentation of the vessels and bile ducts, introduced by Couinaud in the 1950s^[8,9], and the Brisbane 2000 nomenclature is utilized to define minor and major hepatectomy in the field of liver surgery^[10,11]. Minor hepatectomy is defined as the resection of two or fewer Couinaud segments, while major hepatectomy is the removal of three or more Couinaud segments^[11]. The first series on laparoscopic liver resections consisted mostly of minor liver resections^[3,4,12,13]. The first laparoscopic major hepatectomy (LMH) was performed in 1997^[14]. The higher risk for uncontrolled hemorrhage and the requirement of advanced technical expertise, particularly related to major vessel dissection, have slowed the broader adoption of minimally-invasive approaches for major hepatectomy^[15].

The technological advances of our era have also led to the broader implementation of robotics in several fields of surgery, including liver surgery. The ability to obtain three-dimensional and magnified intraoperative vision, the significant decrease in hand tremor, as well as the benefit for the surgeon of operating under more relaxed and comfortable circumstances, have led to a considerable growth in robotic surgery, which can overcome the rigid instrumentation and the limited two-dimensional vision associated with laparoscopic surgery^[16,17]. These characteristics, along with the advent of wristed instruments, can lead to improved dexterity and higher precision in surgical dissection; this is of particular benefit to liver resection, as hilar dissection, curved transection of the liver parenchyma and the resection of lesions in the posterosuperior segments can be more feasible with the use of a robot^[18]. The first large series of robotic liver resection was reported in 2002^[19], and although most current experience is based on minor resections, several studies have reported robotic major hepatectomy (RMH). This review aims to summarize the current state of evidence about the outcomes after LMH vs. RMH. We acknowledge that there is still a very important role for open hepatectomy in cases of multiple bilobar liver tumors or large tumors near critical vascular structures. However, we will focus on the differences between LMH and RMH, as a full review of open major hepatectomy is beyond the scope of this review.

INTERNATIONAL CONSENSUS AND LEARNING CURVES

Before engaging in a head-to-head comparison between LMH and RMH, it is worth mentioning two points that may favor the former approach. First, LMH has been performed for many more years than its robotic counterpart; second, irrespective of the procedural, hospitalization, and total economic cost, the cost of purchasing a robot for a hospital is considerable and has been a major limiting factor to the broader adoption of robotic liver surgery. These two points are of paramount importance, as data suggest that outcomes improve as experience with a surgical approach grows^[20]. It is also worth mentioning that during the second international consensus on laparoscopic liver surgery (Morioka 2014), the jury concluded that laparoscopic minor hepatectomy had at that point already become standard practice, while LMH was still considered to be an innovative procedure still under exploration^[11]. According to the 2018 international consensus statement on robotic hepatectomy, RMH was deemed to be as safe and feasible as both LMH and open major hepatectomy^[21].

For the purpose of this review, we performed a non-systematic search of the PubMed bibliographic database using combinations of the following terms: “laparoscopic”, “robotic”, “minimally invasive”, “hepatectomy”, “major hepatectomy”, “liver resection”, and “major liver resection” (last search March 2020). We included comparative or non-comparative studies reporting on the number of LMH and RMH cases. [Tables 1, 2, and 3](#) present the previously published cases of RMH and LMH^[6,7,12-14,20,22-109], and it is apparent that the experience with LMH is greater than that of the robotic approach.

Table 1. Previously published reports on robotic major hepatectomy

Author	Country/region	Study period	Total number of robotic cases	Robotic major hepatectomy		
				Total major	Left hepatectomy	Right hepatectomy
Giulianotti <i>et al.</i> ^[72] 2011	Italy & USA	Mar 2002-Mar 2009	70	27	5	20
Ji <i>et al.</i> ^[83] 2011	China	Apr 2009-Jul 2009	13	9	6	2
Tsung <i>et al.</i> ^[20] 2014	USA	Nov 2007-Dec 2011	57	21	n/a	n/a
Spampinato <i>et al.</i> ^[94] 2014	Italy	Jan 2009-Dec 2012	25	25	7	16
Yu <i>et al.</i> ^[105] 2014	South Korea	May 2010-Oct 2011	13	3	3	0
Wu <i>et al.</i> ^[22] 2014	Taiwan	Jan 2012-Dec 2012	52	14	0	0
Felli <i>et al.</i> ^[23] 2015	Italy	Apr 2013-May 2014	20	2	2	0
Lee <i>et al.</i> ^[24] 2016	China	Sep 2010-Jan 2015	70	14	10	4
Kingham <i>et al.</i> ^[25] 2016	USA	2010-2014	64	6	4	2
Lai <i>et al.</i> ^[26] 2016	China	May 2009-Feb 2015	100	27	6	20
Lee <i>et al.</i> ^[27] 2016	China	Sep 2010-Apr 2015	15	5	3	2
Sham <i>et al.</i> ^[28] 2016	USA	May 2011-Dec 2014	71	17	n/a	n/a
Chen <i>et al.</i> ^[29] 2016	Taiwan	May 2013-Aug 2015	13	13	0	13
Chen <i>et al.</i> ^[30,31] 2017	Taiwan	Jan 2012-Oct 2015	183	92	32	41
Quijano <i>et al.</i> ^[32] 2017	Spain	Oct 2010-Apr 2016	21	5	2	1
Magistri <i>et al.</i> ^[33] 2017	Italy	Jan 2012-May 2016	22	2	0	2
Efanov <i>et al.</i> ^[34] 2017	Russia	May 2010-Jun 2016	40	2	2	0
Daskalaki <i>et al.</i> ^[35] 2017	USA	Jan 2009-Dec 2013	68	29	2	21
Choi <i>et al.</i> ^[36] 2017	South Korea	Dec 2008-May 2016	70	54	27	12
Khan <i>et al.</i> ^[37] 2018	International	2006-2016	61	16	8	8
Goja <i>et al.</i> ^[38] 2019	India	Feb 2015-Jan 2016	21	6	3	3
Lim <i>et al.</i> ^[39] 2019*	France	2011-2017	61 (55)	9 (4)	n/a	n/a
Marino <i>et al.</i> ^[40] 2019	Italy	Apr 2016-Mar 2017	14	14	0	14
Marino <i>et al.</i> ^[41] 2019	Italy	Apr 2015-May 2017	35	35	35	0
Fruscione <i>et al.</i> ^[42] 2019	USA	2011-2016	57	57	20	20
Gravetz <i>et al.</i> ^[43] 2019	USA	2013-2017	33	8	n/a	n/a
Magistri <i>et al.</i> ^[44] 2019	Italy	Jul 2014-Sep 2017	60	3	1	2
Lee <i>et al.</i> ^[45] 2019	South Korea	Jun 2016-Apr 2018	13	8	8	0
Mejia <i>et al.</i> ^[46] 2020	USA	Aug 2013-Sep 2018	43	8	4	4
Sucandy <i>et al.</i> ^[47] 2020	USA	2013-2018	80	24	14	6
Beard <i>et al.</i> ^[48] 2020*	International	Jan 2008-Oct 2016	115	17	6	9

*Numbers in parentheses represent the number of cases after propensity score-matching. n/a: not available

Table 2. Previously published reports on laparoscopic major hepatectomy

Author	Country/region	Study period	Total number of laparoscopic cases	Laparoscopic major hepatectomy		
				Total major	Left hepatectomy	Right hepatectomy
Huscher <i>et al.</i> ^[14] 1997	Italy	1993-Dec 1995	20	14	6	5
Gigot <i>et al.</i> ^[49] 2002	Europe	Feb 1994-Dec 2000	37	2	n/a	n/a
O'Rourke <i>et al.</i> ^[6] 2004	Australia	Nov 1999-Sep 2002	12	12	0	12
Dulucq <i>et al.</i> ^[50] 2005	France	Jan 1995-Jan 2004	32	11	4	6
Vibert <i>et al.</i> ^[51] 2006	France	Jan 1995-Dec 2004	89	38	3	27
Topal <i>et al.</i> ^[52] 2007	Belgium	n/a	2	2	0	2
Gayet <i>et al.</i> ^[53] 2007	France	n/a	41	41	0	37
Koffron <i>et al.</i> ^[12] 2007	USA	Jul 2001-Nov 2006	300	119	47	64
Dagher <i>et al.</i> ^[54] 2007	France	Feb 1999-Jan 2006	70	19	5	12
Gumbs <i>et al.</i> ^[55] 2008	France	n/a	3	3	0	0
Gumbs <i>et al.</i> ^[56] 2008	France	n/a	5	5	0	0
Cho <i>et al.</i> ^[57] 2008	South Korea	Jan 2004-Dec 2007	128	47	23	13
Buell <i>et al.</i> ^[13] 2008	USA	Jan 2001-Apr 2008	253	69	24	33
Topal <i>et al.</i> ^[58] 2008	Belgium	Oct 2002-Jun 2007	109	21	4	14
Dagher <i>et al.</i> ^[59] 2008	France	Since Feb 1999	20	20	0	20
Wakabayashi <i>et al.</i> ^[60] 2009	Japan	Jul 1995-Apr 2008	176	39	10	12
Castaing <i>et al.</i> ^[61] 2009	France	Jan 1997-May 2007	60	26	0	22

Nguyen <i>et al.</i> ^[62] 2009	USA & Europe	Feb 2000-Sep 2008	109	49	10	31
Vigano <i>et al.</i> ^[63] 2009	France	Jan 1996-Aug 2008	174	35	n/a	23
Bryant <i>et al.</i> ^[64] 2009	France	May 1996-Dec 2007	166	31	11	19
Yoon <i>et al.</i> ^[65] 2009	South Korea	Oct 1998-Jun 2007	46	21	21	0
Cho <i>et al.</i> ^[66] 2009	South Korea	May 2003-Apr 2007	40	12	0	5
Baker <i>et al.</i> ^[67] 2009	USA	Jan 2006-May 2008	33	33	0	33
Dagher <i>et al.</i> ^[68] 2009	International	1997-2008	210	210	74	136
Cai <i>et al.</i> ^[69] 2009	China	2005-2007	19	19	19	0
Dagher <i>et al.</i> ^[70] 2009	France	Feb 2002-Aug 2007	22	22	0	22
Yoon <i>et al.</i> ^[71] 2010	South Korea	Sep 2003-Nov 2008	69	21	2	6
Nitta <i>et al.</i> ^[7] 2010	Japan	Nov 2002-Dec 2008	42	42	16	14
Dagher <i>et al.</i> ^[73] 2010	Europe	1998-2008	163	16	4	10
Martin <i>et al.</i> ^[74] 2010	USA	Jan 2000-Jun 2009	90	90	50	40
Ji <i>et al.</i> ^[83] 2011	China	Apr 2009-Jul 2009	20	4	3	1
Shafae <i>et al.</i> ^[75] 2011	USA & Europe	1997-2009	68	22	1	12
Cho <i>et al.</i> ^[76] 2011	Japan	Aug 2005-Feb 2010	27	20	5	10
Abu Hilal <i>et al.</i> ^[77] 2011	UK	2006-2009	36	36	0	36
Bhojani <i>et al.</i> ^[78] 2012	Canada	Jun 2006-May 2010	57	19	5	8
Topal <i>et al.</i> ^[79] 2012	Belgium	Oct 2002-Dec 2008	20	20	4	13
Cannon <i>et al.</i> ^[80] 2012	USA	2004-2010	35	19	4	14
Gumbs <i>et al.</i> ^[81] 2012	USA	Nov 2008-Oct 2010	53	25	8	13
Abu Hilal <i>et al.</i> ^[82] 2013	UK	Mar 2006-Nov 2011	84	38	0	38
Tsung <i>et al.</i> ^[20] 2014*	USA	Nov 2007-Dec 2011	114	42	n/a	n/a
Spampinato <i>et al.</i> ^[94] 2014	Italy	Jan 2009-Dec 2012	25	25	8	15
Yu <i>et al.</i> ^[105] 2014	South Korea	Jul 2007-Oct 2011	17	11	11	0
Wu <i>et al.</i> ^[22] 2014	Taiwan	Jan 2012-Dec 2012	69	4	0	0
Medbery <i>et al.</i> ^[84] 2014	USA	May 2008-Mar 2012	48	48	0	48
Zhang <i>et al.</i> ^[85] 2014	China	July 2011-Mar 2013	25	25	0	25
Ahn <i>et al.</i> ^[86] 2014	South Korea	Jan 2005-Feb 2013	51	2	2	0
Benkabbou <i>et al.</i> ^[87] 2015	Morocco	Jun 2010-Feb 2013	13	2	1	1
Xiao <i>et al.</i> ^[88] 2015	China	Jan 2010-Dec 2012	41	4	0	0
Takahara <i>et al.</i> ^[89] 2015*	Japan	2000-2010	436 (387)	46 (42)	n/a	n/a
Allard <i>et al.</i> ^[90] 2015	France	Jan 2006-Dec 2013	176	80	14	63
Beppu <i>et al.</i> ^[91] 2015*	Japan	Jan 2005-Dec 2010	210 (171)	12 (10)	n/a	n/a
de'Angelis <i>et al.</i> ^[92] 2015	France	Jan 2000-Dec 2013	52	18	2	15
van der Poel <i>et al.</i> ^[93] 2016	UK	Aug 2003-Mar 2015	159	159	54	105
Lee <i>et al.</i> ^[24] 2016	China	Nov 2003-Jan 2015	66	2	2	0
Lai <i>et al.</i> ^[26] 2016	China	Oct 1998-Feb 2015	35	1	0	1
Takahara <i>et al.</i> ^[95] 2016	Japan	Jan 2011-Dec 2013	929	929	238	234
Cipriani <i>et al.</i> ^[96] 2016	UK	Aug 2004-Apr 2015	133	65	8	43
Ratti <i>et al.</i> ^[97] 2016	Italy	2008-2014	25	6	4	2
Tranchart <i>et al.</i> ^[98] 2016	International	1997-2013	89	7	3	4
Untereiner <i>et al.</i> ^[99] 2016	France	Jan 2012-Jan 2015	18	2	2	0
Komatsu <i>et al.</i> ^[100] 2016	France	Jan 2006-May 2014	38	38	10	28
Martinez-Cecilia <i>et al.</i> ^[101] 2017*	Europe	Jan 2005-Dec 2012	287 (225)	49 (47)	n/a	n/a
Sotiropoulos <i>et al.</i> ^[102] 2017	Greece	Jan 2012-Jan 2017	42	1	1	0
Peng <i>et al.</i> ^[103] 2017	China	Jan 2013-Oct 2016	36	15	15	0
Chen <i>et al.</i> ^[104] 2017	China	Apr 2015-Sep 2016	225	126	26	43
Efanov <i>et al.</i> ^[34] 2017	Russia	May 2010-Jun 2016	91	11	2	9
Lim <i>et al.</i> ^[39] 2019*	France	2011-2017	111 (55)	15 (8)	n/a	n/a
Marino <i>et al.</i> ^[40] 2019	Italy	Apr 2016-Mar 2017	20	20	0	20
Fruscione <i>et al.</i> ^[42] 2019	USA	2011-2016	116	116	22	46
Jang <i>et al.</i> ^[106] 2019	South Korea	Jan 2014-Jul 2017	37	17	9	8
Cipriani <i>et al.</i> ^[107] 2019	Italy	Jan 2005-Nov 2017	145	145	59	86
Chen <i>et al.</i> ^[108] 2019	Taiwan	Dec 2010-Dec 2016	436	90	31	52
Lee <i>et al.</i> ^[45] 2019	South Korea	Jun 2016-Apr 2018	10	3	3	0
Mejia <i>et al.</i> ^[46] 2020	USA	Jun 2005-Sep 2018	171	46	13	33
Cipriani <i>et al.</i> ^[109] 2020	Europe	Jan 2007-Feb 2016	597 (545)	597 (545)	215 (172)	382 (351)
Beard <i>et al.</i> ^[48] 2020*	International	Jul 2002-Oct 2017	514 (115)	53 (21)	17 (n/a)	33 (n/a)

*Numbers in parentheses represent the number of cases after propensity score-matching. n/a: not available

Table 3. Previously published reports on the comparison of laparoscopic and robotic liver resection along with the number of major hepatectomy cases in each group

Author	Total laparoscopic	Laparoscopic major hepatectomy	Total robotic	Robotic major hepatectomy
Ji <i>et al.</i> ^[83] 2011	20	4	13	9
Tsung <i>et al.</i> ^[20] 2014	114	42	57	21
Spampinato <i>et al.</i> ^[94] 2014	25	25	25	25
Yu <i>et al.</i> ^[105] 2014	17	11	13	3
Wu <i>et al.</i> ^[22] 2014	69	4	52	14
Lee <i>et al.</i> ^[24] 2016	66	2	70	14
Lai <i>et al.</i> ^[26] 2016	35	1	100	27
Efanov <i>et al.</i> ^[34] 2017	91	11	40	2
Lim <i>et al.</i> ^[39] 2019*	111 (55)	15 (8)	61 (55)	9 (4)
Marino <i>et al.</i> ^[40] 2019	20	20	14	14
Fruscione <i>et al.</i> ^[42] 2019	116	116	57	57
Lee <i>et al.</i> ^[45] 2019	10	3	13	8
Mejia <i>et al.</i> ^[46] 2020	171	46	43	8
Beard <i>et al.</i> ^[48] 2020*	514 (115)	53 (21)	115	18

*Numbers in parentheses represent the number of cases after propensity score-matching

Determining the learning curve for each approach is also of major significance. The learning curve is “the improvement in performance over time or the change in the ability to complete a task until failure is decreased to a constant acceptable rate”^[110]. Data suggest that the learning curve for LMH is around 45-60 cases^[93,111-113]. van der Poel *et al.*^[93] reported that 55 is the “golden” number for LMH; however, all surgical operations were performed by two experienced hepatobiliary surgeons with at least three years of additional experience on minor laparoscopic hepatectomy. For RMH, Chen *et al.*^[30] described an initial phase of 15 patients followed by an intermediate phase of 25 patients. The accumulated experience of the first 15 cases (defined as the “initial learning curve”), mostly comprised of right and left hemihepatectomies, was followed by more complex cases, such as trisectionectomy and 8-5-4 trisegmentectomy, in the next 25 cases (“phase of increased competency”). Their last 52-case “matured phase” was associated with an overall improvement in outcomes. However, the authors did not mention who their “learning curve” refers to, as “all procedures were performed by the same operative team”, but they do not specify their prior experience with minor robotic resections or even with LMH. Tsung *et al.*^[20] reported that the outcomes of their robotic cases between 2010-2011 were superior to those of the robotic cases between 2007-2010, but the authors pooled together both minor and major resections for this comparison.

OPERATING TIME

A systematic review and pooled analysis of outcomes on robotic liver resections showed that the mean operating time for RMH (≥ 4 segments) was 405 ± 100 min^[18], while another more recent systematic review reported similar pooled mean operating time for RMH (≥ 3 segments) of 403.4 ± 107.5 min^[114]. A systematic literature review on LMH^[115] showed that mean operating time in all individuals studies was lower than the pooled operating times reported in the RMH systematic reviews^[18,114]. Additionally, in a systematic review comparing LMH to open major hepatectomy, the pooled mean operating time in the LMH arm was 285 ± 105.6 min^[116]. Similarly, in a large multicenter study from Europe, Cipriani *et al.*^[109] reported a median operating time of 300 min (IQR 205-380) for LMH, and more specifically 300 min (IQR 240-402) for right hepatectomy and 270 min (IQR 160-290) for left hepatectomy. Tsung *et al.*^[20] compared RMH vs. LMH, and showed that both overall operating room time (452 min vs. 348.5 min) and operating time (330 min vs. 280.5 min) were significantly longer in the RMH group. Spampinato *et al.*^[94] also showed that operating time was longer in RMH (430, IQR 240-725 min) when compared to LMH (360, IQR 180-600 min), while all procedures were performed by surgeons experienced in minimally-invasive liver surgery. Notably, a more recent study showed no difference in median operating time between RMH (194, range 152-255 min) and LMH (204, 149-280 min), and all of the operations were again performed by experienced minimally-invasive

hepatobiliary surgeons^[42]. A Korean group recently published the initial experience of a single surgeon with robotic liver surgery and showed that there was no difference in operating time between robotic and laparoscopic left hepatectomy (248.6 ± 37.5 min vs. 226.7 ± 26.6 min)^[43]. Another recent study comparing robotic vs. laparoscopic right hepatectomy demonstrated that operating time was significantly shorter in the robotic group compared to the laparoscopic one (425 ± 139 min vs. 565.18 ± 183.73 min), and all procedures were performed by the same young surgeon^[40]. That may serve as an indicator that as experience with RMH grows, operating time seems to decrease and to be equivalent to, or even shorter than, that of LMH. However, a major confounding factor is surgeon's surgical expertise and prior experience with minimally-invasive major hepatectomy; thus, future studies comparing operating time, as well as other parameters, between RMH and LMH should always mention primary surgeon's prior experience and should make sure that the two comparison groups are equivalent regarding this parameter.

ESTIMATED BLOOD LOSS

The pooled estimated blood loss (EBL) in RMH based on two systematic reviews was 543.4 ± 371 mL^[114] and 380 ± 505 mL^[18], respectively. The pooled mean EBL for the LMH arm in a systematic review comparing LMH to open major hepatectomy was 450.6 ± 563.2 ^[116], which is comparable to the pooled rates reported in the RMH systematic reviews^[18,114]. However, major deviations were found between the individual RMH or LMH studies themselves included in each systematic review. Cipriani *et al.*^[109] reported a median EBL of 350 mL (IQR 125-1350) for LMH, and more specifically 400 mL (IQR 200-800) for right hepatectomy and 300 mL (IQR 50-260) for left hepatectomy. Studies directly comparing EBL between RMH and LMH showed that EBL in RMH was lower than that in LMH, while the difference was not statistically significant in any of the individual studies^[20,40,42,94].

LENGTH OF STAY

Two prior systematic reviews on RMH reported a pooled mean hospital length of stay (LOS) of 10.5 ± 4.8 ^[114] and 11 ± 6 days^[18], respectively. The mean LOS of most individual studies included in a systematic review on LMH^[115] was shorter than that of the two RMH systematic reviews. Another systematic review showed that the pooled mean LOS for LMH was 10 ± 8.7 days^[116]. Cipriani *et al.*^[109] reported a median LOS of 6 days (IQR 4-10) for LMH, and more specifically 7 days (IQR 4-13) for right hepatectomy, and 5 days (IQR 4-10) for left hepatectomy. Studies reporting on the direct comparison of RMH vs. LMH did not demonstrate any statistically significant difference between the two arms^[20,40,42,94].

COMPLICATIONS, SURVIVAL AND ONCOLOGIC OUTCOMES

When comparing RMH and LMH, Tsung *et al.*^[20] reported that no difference was observed between the two groups with a complication rate of 24% ($n = 5/21$) vs. 32% ($n = 13/42$), respectively, while only one patient in the RMH group experienced a major complication (Clavien-Dindo grade ≥ 3) (4.8% vs. 0%, respectively). The 90-day mortality rate was 0% in both groups^[20]. Similar complication rates were documented by Spampinato *et al.*^[94] RMH: 20% ($n = 5/25$) vs. LMH: 36% ($n = 9/25$), with 4% ($n = 1/25$) and 12% ($n = 3/25$) of the patients experiencing a major complication (Clavien-Dindo grade ≥ 3), respectively. However, one patient in the LMH group died^[94]. Marino *et al.*^[40] also failed to show a difference in morbidity with 21.4% ($n = 3/14$) of the patients in the RMH arm vs. 15% ($n = 3/20$) in the LMH group experiencing any complications, while no major complications occurred. Ninety-day mortality was 0% in both groups^[40]. The largest and most recent comparative study between RMH and LMH was performed by Fruscione *et al.*^[42] and also did not show a significant difference in complications between the two groups. Specifically, the complication rate for RMH was 28.1% ($n = 16/57$) and for LMH 35.3% ($n = 41/116$), with 7% ($n = 4/57$) and 9.5% ($n = 11/116$) being classified as major complications (Clavien-Dindo grade ≥ 3). No death was reported in either of the comparison arms^[42]. Additionally, when RMH and LMH were performed for liver malignancies, none of the four studies showed a difference in surgical margin status between the two approaches (positive margins: 0%-8.3% vs. 7%-15%, respectively), and long-term outcomes were comparable when reported^[20,40,42,94].

ECONOMIC COST

Mejia *et al.*^[46] reported that the adjusted room and board charges were significantly lower in the LMH *vs.* the RMH group, with no other difference between the two groups regarding economic cost. Of note, when comparing the cost of LMH *vs.* RMH, the fixed capital cost (\$1,000,000-\$2,600,000 for a robotic system with a 10-year longevity period)^[117-120] and annual maintenance cost (\$90,000-\$175,000)^[120] for a hospital to purchase and maintain a surgical robot, should also be taken into consideration. The addition of this cost can be burdensome, particularly for low-volume liver surgery centers, and this remains a significant driving factor for the slow spread of RMH and robotic liver surgery in general. It should also be noted that access to the robot in the operating room can be a challenge due to competition with other surgical service lines.

CONCLUSION

The introduction of laparoscopy and robotic surgical systems in liver surgery has significantly changed the current state of practice. Although both approaches have been more widely tested for minor liver resections, the number of LMHs and RMHs performed worldwide has significantly increased over recent years, and is still on the rise. Although there is a considerable deviation in outcomes after RMH, especially during early experience, when RMH is performed by experienced surgeons in high-volume liver centers, it can be associated with equivalent operating time, EBL, LOS, morbidity and mortality, and comparable oncologic outcomes in terms of achieving a margin-negative resection and long-term overall survival. The fixed capital and annual maintenance costs for the robotic surgical system may pose a significant obstacle in the broader adoption of RMH, particularly in low-volume centers.

DECLARATIONS

Authors' contributions

Study concept, data acquisition, data analysis and interpretation, drafting, critical revision, final approval of the manuscript: Ziogas IA, Tohme S, Geller DA

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All authors declared that there are no conflicts of interest.

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Not applicable.

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Review

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Percutaneous “edge-to-edge” leaflet repair in patient with primary mitral valve regurgitation

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Abstract

Mitral regurgitation (MR) is the most common left-sided heart valve disease in developed countries with a constantly rising number of patients requiring hospitalization or intervention. Organic MR is defined as a primary structural abnormality of the mitral valve (MV) apparatus which may be caused by a broad set of pathological processes, among which myxomatous degeneration of the leaflets causing MV prolapse is the most common. If left untreated, chronic severe MR leads to serious adverse outcomes, from heart failure to death, but medical therapy is unable to change the natural history of the disease. Surgical correction, by means of valve repair or replacement, is the gold standard for the treatment of symptomatic patients with severe primary MR. However, surgery is not feasible for a large percentage of patients because of old age, reduced left ventricular ejection fraction and the presence of severe comorbidities. Therefore, in recent years, several percutaneous therapeutic alternatives suitable for high or prohibitive surgical risk patients were developed. In this review we discuss the transcatheter treatment of primary MR, from available evidence to technical practice, with a focus on the percutaneous “edge-to-edge” leaflet repair performed with the MitraClip System and the PASCAL Repair System.

Keywords: Degenerative mitral valve disease, mitral regurgitation, mitral insufficiency, MitraClip, PASCAL

INTRODUCTION

Mitral regurgitation (MR) is the most common left-sided heart valve disease in developed countries with a prevalence that increases with age (from 0.5% among subjects 18-44 years old to 9.3% in the population



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over 75 years of age), which in the last decades has led to a sharp rise in the number of patients requiring hospitalization or intervention^[1]. It is acknowledged that an organic (or primary) and a functional (or secondary) etiology of MR can be distinguished, and these two entities carry different prognosis and management^[2]. The purpose of the current review is to outline the percutaneous treatment of primary MR, from available evidence to technical practice, with a focus on transcatheter “edge-to-edge” leaflet repair.

ETIOLOGY AND TREATMENT OF PRIMARY MR

Organic MR is defined as a primary structural abnormality of the mitral valve (MV) apparatus. Its etiology is largely dominated by myxomatous degeneration of the leaflets (which ranges from fibroelastic deficiency to Barlow’s disease), followed by rheumatic disease, infective endocarditis, connective tissue and ischemic disease, congenital malformations, and iatrogenic (radiation therapy or drugs) and traumatic lesions^[3,4]. Fibroelastic deficiency usually presents with thin transparent leaflets with focal prolapse or flail due to chordal rupture, while Barlow’s disease hallmarks are multi-segment prolapse involving one or both leaflets in a valve with significant myxomatous changes, excess leaflet tissue and dilated annulus. Between these two phenotypes, a broad spectrum of degenerative disease is found in clinical practice^[5]. Regardless of the anatomical background, MV prolapse is the most common cardiac valvular anomaly in developed countries affecting approximately 2% of the general population. It is associated with a variable degree of MR, with most patients having trivial or mild regurgitation; previous studies have found a 6% prevalence of a severe degree of the disease in the outpatient population with valve prolapse^[6,7]. However, very little data are available in these patients regarding the progression of MR severity and the associated risk factors^[8,9]. Left untreated, chronic severe MR may lead to left ventricular (LV) remodeling because of volume overload, myocardial dysfunction, heart failure, left atrial dilatation, atrial fibrillation and pulmonary hypertension. Surgical correction, by means of valve repair or replacement, is the gold standard for the treatment of symptomatic patients with severe primary MR^[2]. The optimal timing for intervention has to be according to symptom onset, worsening of LV function, significant LV dilatation, or development of atrial fibrillation or pulmonary hypertension. Despite the lack of randomized clinical trials comparing the results of valve replacement and repair, it is widely accepted that valve repair is the preferred treatment, when it is feasible when and a durable repair is likely^[2]. However, symptomatic patients are frequently denied surgical treatment mainly because of impaired LV ejection fraction, older age and comorbidities^[3,10]. Therefore, in recent years, great effort was made to develop less invasive, percutaneous therapeutic alternatives suitable for high or prohibitive surgical risk patients. Possible catheter-based approaches for the treatment of MR include transapical or transseptal valve repair or replacement, placement of annular tightening devices, and insertion of artificial chordae. The “edge-to-edge” surgical repair technique, making a “double-orifice” MV, was the first to be adapted for the percutaneous approach with the MitraClip System (Abbott Vascular, Santa Clara, CA, USA), reaching over time more than 70,000 implants worldwide, since its first use in humans in 2003^[11]. Later in 2019, the new PASCAL repair system (Edwards Lifesciences, Irvine, CA, USA) received CE mark for the percutaneous “edge-to-edge” repair treatment of MR, further expanding the therapeutic options available to the interventional cardiologist and the population eligible for treatment. As a matter of fact, current guidelines recommend a percutaneous edge-to-edge repair for the treatment of patients with symptomatic moderate-to-severe or severe primary MR who fulfill echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team evaluation (Class IIB, LOE C)^[2].

TECHNICAL ASPECTS OF TRANSCATHETER MV “EDGE-TO-EDGE” LEAFLET REPAIR

Proper patient selection with preoperative echocardiography using both 2D and 3D transesophageal echocardiography (TEE) is mandatory to confirm MR severity and define its mechanism while evaluating anatomic eligibility for an “edge-to-edge” transcatheter repair and, ultimately, achieve satisfactory results^[2,12]. In the early years of MitraClip usage, eligibility was evaluated according to the preliminary

Table 1. Classification of MV morphology based on anatomical criteria for MitraClip implantation procedure

Optimal valve morphology Beginner operator	Possible valve morphology Average operator	Tough/unsuitable valve morphology Expert operator
Central pathology (A2/P2 scallops)	Commissural pathology (A1/P1 or A3/P3 scallops)	Barlow's syndrome, flail in multiple scallops
No calcification	Mild calcification outside grasping zone, annulus calcification, previous annuloplasty	Significant calcification of grasping zone
MVA > 4 cmq	MVA > 3 cmq, preserved mobility	-
Posterior leaflet length ≥ 10 mm	Posterior leaflet length 7-10 mm	Posterior leaflet length < 7 mm
Tenting height < 11 mm	Tenting height > 11 mm	-
Normal leaflet thickness and mobility	Restricted leaflet motion during systole	Restricted leaflet motion during systole and diastole, rheumatic disease
Flail gap < 10 mm and width < 15 mm	Flail width > 15 mm with dilated annulus (multiple clip implantation)	-

MV: mitral valve; MVA: mitral valve area

EVEREST trial inclusion and exclusion criteria^[13]; nowadays, thanks to the spread of the procedure, the growing experience of the operators and several technical improvements have allowed broadening the spectrum of suitable MV lesions, including some that were previously considered not feasible with good results, particularly in high-volume centers. Therefore, concerning eligibility for the procedure, MV anatomies may be divided into “optimal”, “challenging” and “advanced”, requiring increasing operator experience. Absolute contraindications to the percutaneous “edge-to-edge” technique are still represented by very short posterior leaflet, high degree of calcification in leaflet grasping area, MV area < 3 cm² and rheumatic MR^[14] [Table 1]. An interesting topic is the management of MR of mixed or undetermined etiologies, but data in this regard are still scant. To date, only few registries report an incidence ranging from 3% to 10% in real-world practice; however, their results have focused only on degenerative and functional etiology for outcome data analysis. As a matter of fact, standardized criteria to define a “mixed etiology” are lacking, making it difficult to achieve a shared definition among different studies, and in most cases a predominant etiology between organic and functional may be individualized with a careful multiparametric evaluation, allowing classification of the MR into one of the two dichotomous categories.

The MitraClip System consists of a 24 Fr guide catheter and a clip delivery system, which includes one detachable clip [Figure 1]. The system is steerable using two knobs, which allow medial-lateral and anterior-posterior deflection; moreover, the clip delivery system includes a control mechanism by which the clip arms are opened and closed. The procedure is performed in the catheterization laboratory, under general anesthesia and with fluoroscopic and TEE guidance. A transseptal approach is used, and the puncture has to be performed in the posterosuperior part of the fossa ovalis, 4.5 cm ± 0.5 cm from the MV plane, to guarantee optimal maneuverability of the clip delivery system in the left atrium. Therefore, the clip is aligned on the main regurgitation jet, perpendicularly to the MV line of coaptation. Subsequently, arms are opened with a 180° angle, grippers are raised, the system is advanced into the LV and then retracted until reaching a position where firm grasping of both leaflets can be expected. Finally, the leaflets are grasped with grippers and clip arm closure and the presence of adequate “tissue-bridge” inside the device as well as the amount of residual MR and mitral gradient need to be evaluated. If the result is acceptable, the device is deployed by maneuvering the clip delivery system. If needed, particularly in complex anatomies (i.e., cleft, commissural flail, Barlow's disease, etc.), more than one clip may be positioned. In this case, residual MR and transvalvular gradients must be re-assessed for each additional clip. Main possible complications of the procedure include peripheral vascular injury, injury of surrounding cardiac structures during transseptal puncture, potentially causing cardiac tamponade requiring pericardiocentesis, clip detachment and embolization or clip entanglement in the chordae tendineae with possible damage^[15].

Compared to the first-generation device that was launched in 2008, the current generation includes two different versions: the MitraClip NT_R and the MitraClip XT_R. The former is an evolution of the previous

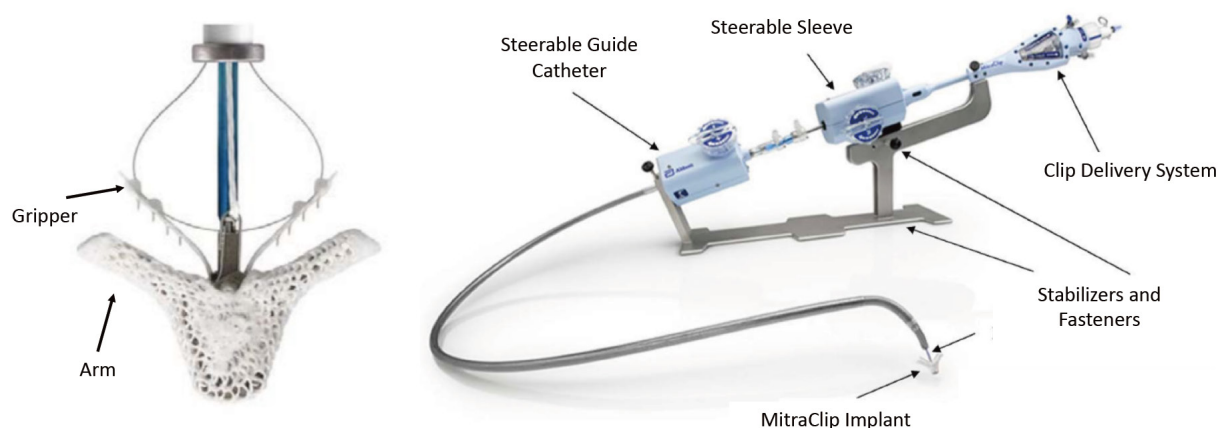


Figure 1. In the left panel, the MitraClip device is shown in its open configuration with grippers opened. Right panel shows the delivery system, consisting of a Steerable Guide Catheter and the Clip Delivery System (Steerable Sleeve, Delivery Catheter and Clip) which are steered and actuated using control knobs, levers and fasteners located on the handles

generation device (the MitraClip NT) with an enhanced delivery system, whereas the latter is a completely new version, with larger and longer arms and grippers that should allow a deeper and more stable grasping, particularly in case of large coaptation gaps or redundant MV tissue, frequently encountered in the degenerative settings.

The PASCAL Repair System consists of a 10-mm central spacer, intended to fill the regurgitation area, and two broad paddles intended to maximize leaflet coaptation and reduce stress on the grasping area (when closed, the paddles also dynamically flex on every heartbeat, as the valve opens and closes). The implant has clasps that allow for independent leaflet capture and offer the possibility to fine-tune leaflet positioning. The 22 Fr delivery system includes three catheters: a guide sheath, a steerable catheter, and an implant catheter used to deliver the implant. The three independent catheter movements in all planes allow access to different locations across the coaptation line and a very simple control of position and orientation of the device [Figure 2]. All these features were designed to overcome some of the technical limitations of the MitraClip system in complex anatomies, such as short posterior leaflet, large flail gaps, severe tethering, and severe annular dilatation^[16]. Specifically, in a degenerative mitral regurgitation (DMR) setting: the independent catheters should simplify the navigation in the left atrium and the orientation of the device; the larger size of the implant should achieve effective MR reduction; and the wide paddles and optional independent leaflet grasping should ensure reaching a straight leaflet insertion in case of challenging anatomies, with no determinant impact on post-procedural MV gradient. However, further studies are needed to assess the safety and effectiveness of this novel device in this complex anatomical setting.

EVIDENCE ON PERCUTANEOUS “EDGE-TO-EDGE” LEAFLET TREATMENT IN PRIMARY MR

Current evidence about the efficacy and safety of the MitraClip in the setting of organic MR is mostly based on the initial EVEREST cohort, the EVEREST II randomized trial and single or multicenter world-wide registries [Table 2]. The EVEREST pilot study enrolled 107 patients, of which 79% presented with degenerative MR. Acute procedural success occurred in 74% of recruited patient and 9% experienced major adverse events (MAE) at 30-day follow-up. The primary efficacy endpoint, a composite of freedom from death, MV surgery and residual MR > 2+, occurred in 66% of the population at 1 year and remained stable at 2 and 3-year of follow up^[13], while 30% of patients had MV surgery up to 3 years after the clip procedure. In the randomized EVEREST II trial, the MitraClip system was compared to conventional MV surgery; 279 patients were enrolled and almost one-third of the population had complex degenerative MR with either Barlow’s disease or anterior leaflet prolapse. The MitraClip procedure was associated with lower MAE incidence at 30 days follow-up (48% vs. 15%, $P < 0.001$). This primary safety endpoint was defined as the composite of death, myocardial infarction, reoperation for failed mitral valve surgery, nonelective

Table 2. Real-world registries on safety and efficacy results of the MitraClip procedure

Registry	No. of pts.	Age	Primary MR	Procedural success	30-day mortality	1-year mortality	1-year MR grade $\leq 2+$	1-year NYHA class $\leq II$
REALISM ^[26]	351	76 \pm 11	30%	86%	5%	23%	83.6%	82.9%
ACCESS-EU ^[27]	567	74 \pm 10	23%	91%	3%	17%	78.9%	71.4%
SENTINEL ^[28]	628	74 \pm 10	23%	95%	-	15%	94%	74.2%
TRAMI ^[15,29]	828	76 (71-81)	29%	97%	5%	20%	-	63.3%
GRASP-IT ^[30]	304	72 \pm 10	21%	92%	3%	13%	-	-
STS/ACC TVT ^[31]	2952	82 (74-86)	86%	92%	5%	26%	-	-
MITRA-SWISS ^[32]	100	72 \pm 12	38%	85%	-	15%	78%	80%

pts: patients; MR: mitral regurgitation; NYHA: New York Heart Association

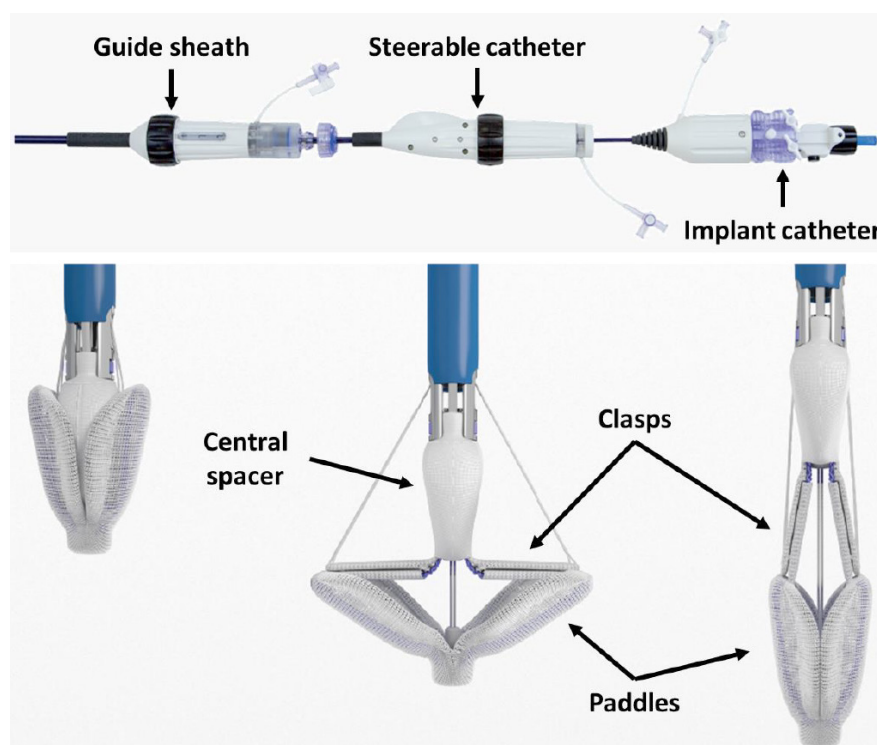


Figure 2. Upper panel shows the PASCAL Delivery System handle, comprising three different parts, one for each catheter. Independent movement of the three catheters is actuated by the use of control knobs. Lower panel shows the PASCAL implant in the closed, opened and elongated configurations (from left to right, respectively)

cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 h, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood; to note, the former was the major driver of superiority for the MitraClip procedure. When considering any MAE excluding transfusion, no significant differences were observed between surgical and percutaneous treatment. At 12 months follow-up, the primary efficacy endpoint was greater in the surgical group compared to the percutaneous group (respectively 73% vs. 55%, $P = 0.007$) but with similar improvements in clinical outcomes such as LV size, New York Heart Association (NYHA) functional class and quality of life measures^[17]. At a longer follow-up, patients requiring surgery for residual MR or MV dysfunction during the first year after treatment were more commonly those initially treated with percutaneous repair, but comparably low rates of surgery were observed in both groups between 1- and 5-year follow-up^[18]. More recently, Buzzatti *et al.*^[19] showed lower acute postoperative complications and improved 1-year survival after MitraClip treatment compared to surgery in elderly patients (age > 75) affected by primary MR and STS-PROM $< 8\%$. However, the percutaneous procedure was once again associated with greater MR recurrence and reduced survival

beyond 1 year of follow-up. As a matter of fact, current clinical guidelines still recommend surgical valve repair as the gold standard for the treatment of primary MR, restricting the percutaneous “edge-to-edge” option to patients judged inoperable or at high surgical risk^[2]. In this population, improvements in quality of life, NYHA functional class, LV reverse remodeling and reduction in heart failure hospitalizations are consistently observed after treatment with MitraClip^[20]. Data on the new MitraClip XT_R are still limited to initial experiences in selected patients with DMR and complex MV anatomies, such as Barlow’s disease^[21,22]. A large observational prospective study, the MitraClip EXPAND Study (NCT03502811) is designed to enroll up to 1000 patients to confirm the safety and performance of the NT_R and XT_R System, identifying trends in patient selection for MitraClip therapy in a real-world use.

Current data about the PASCAL Repair System are limited to the first-in-man study, which enrolled 23 patients^[16], and the CLASP study, a multicenter prospective single-arm study in 62 patients with primary and secondary moderate-to-severe or severe MR (36% of degenerative etiology)^[23]. In the latter, successful implantation was achieved in 95% of patients. At 30 days, encouraging results were shown, with a MAE rate of 6.5%, with an all-cause mortality rate of 1.6% and no occurrence of stroke; procedural residual MR grade 2+ or less was achieved in 98% patients, and 85% were in NYHA functional class I or II. The mean 6-min walk distance increased by 36 m from baseline and both the Kansas City Cardiomyopathy Questionnaire and EQ-5D Health Questionnaire scores improved significantly. Further results collecting 6-month and 1-year follow-up have been recently presented showing sustained results compared to the previous one^[24,25]. The forthcoming Edwards PASCAL CLASP IID/IIF Pivotal Clinical Trial (CLASP IID/IIF; NCT03706833) is the first randomized controlled trial that is going to specifically investigate the safety and effectiveness of the PASCAL system compared to the MitraClip system in patients with degenerative MR at high or prohibitive risk for MV surgery by the Heart Team.

CASE EXAMPLE: PRIMARY MR TREATED WITH THE MITRACLIP SYSTEM

We report here the case of a 75-year-old man affected by symptomatic severe degenerative MR and a history of hypertension, paroxysmal atrial fibrillation and ischemic cardiopathy initially treated with triple coronary artery bypass graft and later with percutaneous coronary stenting on left main and circumflex artery because of venous graft occlusion. He also underwent mechanical aortic valve prosthesis implantation because of severe aortic insufficiency and several comorbidities, including beta-thalassemia minor with moderate-to-severe anemia often requiring blood transfusions, chronic obstructive pulmonary disease, kyphoscoliosis, left kidney atrophy with chronic renal insufficiency and previous thoracic radiotherapy and splenectomy for the treatment of a Hodgkin’s lymphoma. A 2D and 3D transthoracic echocardiogram showed a normal-sized left ventricle with preserved EF and unchanged regional wall motion abnormalities, a well-functioning mechanical aortic prosthesis and a severe MR due to P2 leaflet prolapse extended to P3 and a P1-P2 cleft. Of note, calcification of the anterior leaflet was present outside the grasping area reducing mobility and producing a mean gradient of 3 mmHg. Left atrium was severely dilated, and a moderate tricuspid regurgitation was also detected, with a mean arterial pressure of 37 mmHg. These findings were confirmed with 2D and 3D TEE, which allowed us to positively assess anatomic suitability of MitraClip implant [Figure 3]. After multidisciplinary Heart Team clinical evaluation, the patient became a suitable candidate for percutaneous “edge-to-edge” repair, with an intended treatment strategy of implantation of two convergent clips. The procedure was carried out through a right femoral venous access and under fluoroscopic and both 2D and 3D TEE guidance. The transseptal puncture was done in a posteriosuperior position of the fossa ovalis with a measured height of 4.3 cm over the atrioventricular plane. A guidewire was then positioned in the left superior pulmonary vein and the MitraClip delivery system was advanced into the left atrium [Figure 4]. Subsequently, the first clip was aligned on the main regurgitation jet in A2-P2 position with a slight counterclockwise orientation, arms were opened with a 180° angle, grippers were raised, and the clip was advanced into the left ventricle. The system was then retracted to reach a stable grasping of both leaflets and clip arms were closed [Figure 5]. Therefore, after a careful TEE final assessment, the first clip was deployed. The same procedural steps were repeated for the placement of a

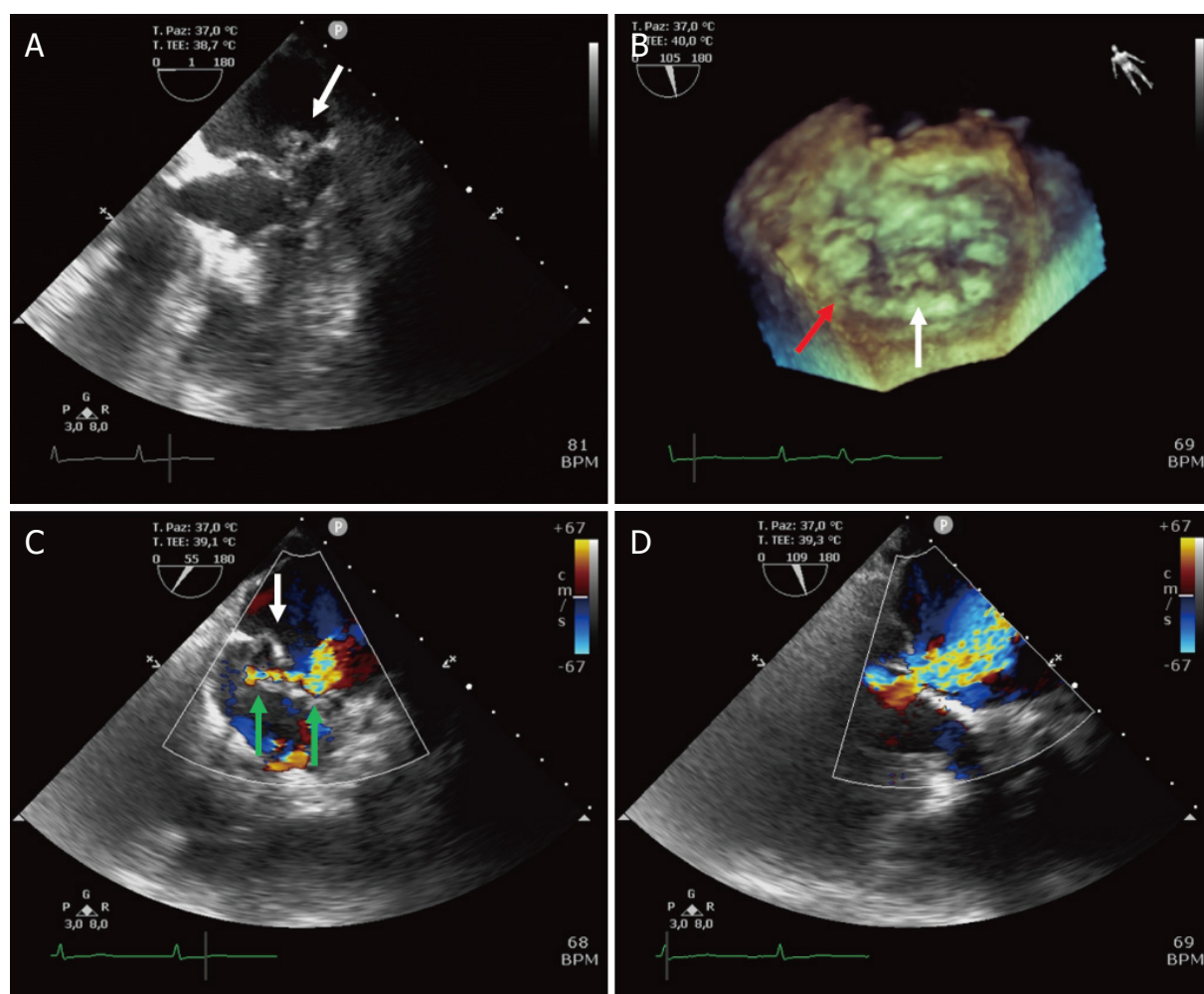


Figure 3. Preoperative evaluation with 2D (A, C, D) and 3D (B) TEE. White arrows indicate P2 prolapse; red arrow indicates P1-P2 cleft. Color TEE (C, D) shows 2 regurgitation jets (green arrows) with the main one localized at the level of P2 prolapse, producing severe mitral regurgitation

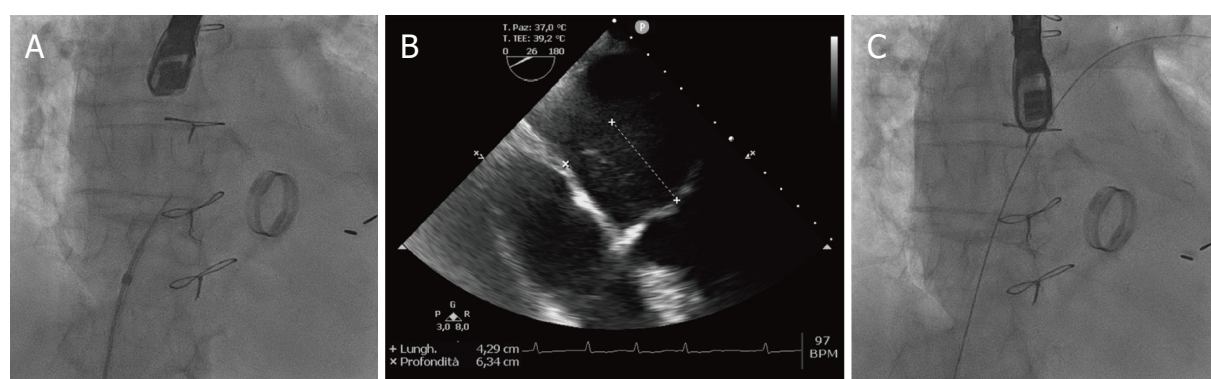


Figure 4. Transseptal puncture under fluoroscopic (A) and TEE (B) guidance. A puncture 4 to 4.5 cm above the MV plane in a posterosuperior position allows good maneuverability of the delivery system. After the transseptal puncture, a guidewire is introduced in the left atrium and then in the left superior pulmonary vein (C)

second clip lateral to the first one, with a slight clockwise orientation, in P1-A2 position [Figure 6]. At the end of the procedure, mild residual MR was detected with a mean gradient less than 5 mmHg [Figure 7].

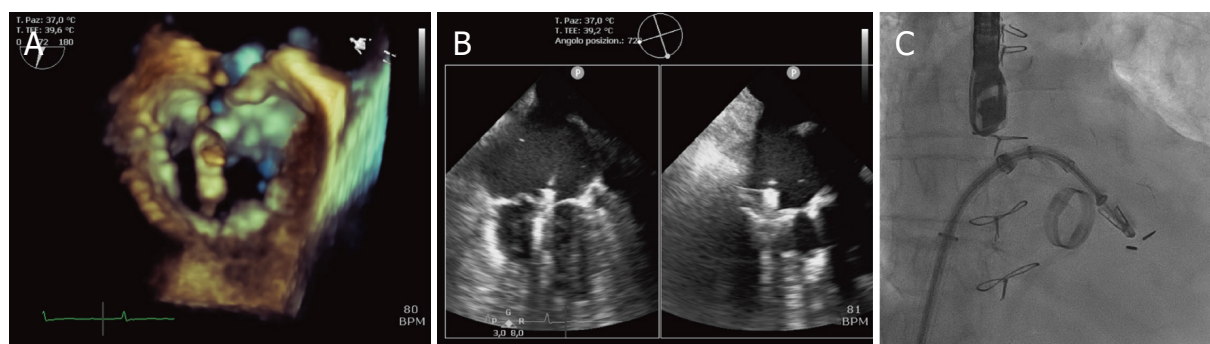


Figure 5. Implantation of a first MitraClip. The device is aligned with the main regurgitation jet at P2 prolapse, perpendicularly to the coaptation plane and slightly oriented counterclockwise (A); under TEE (B) and fluoroscopic (C) guidance, clip arms are opened, the device is advanced in the left ventricle and then retracted to grasp both leaflets

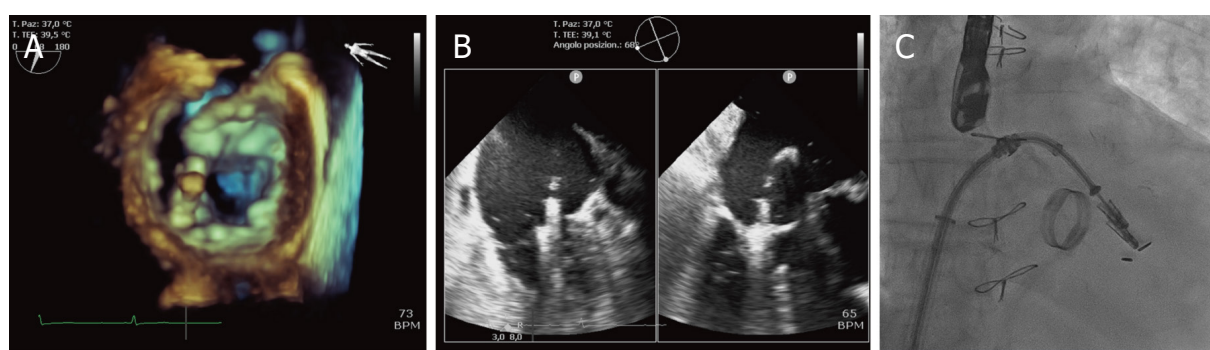


Figure 6. Implantation of a second MitraClip. The second device is placed in P1-A2 position with a slight clockwise orientation compared to the first Clip (convergent clip technique) under 3D TEE (A), X-plan view on TEE (B) and fluoroscopic (C) guidance

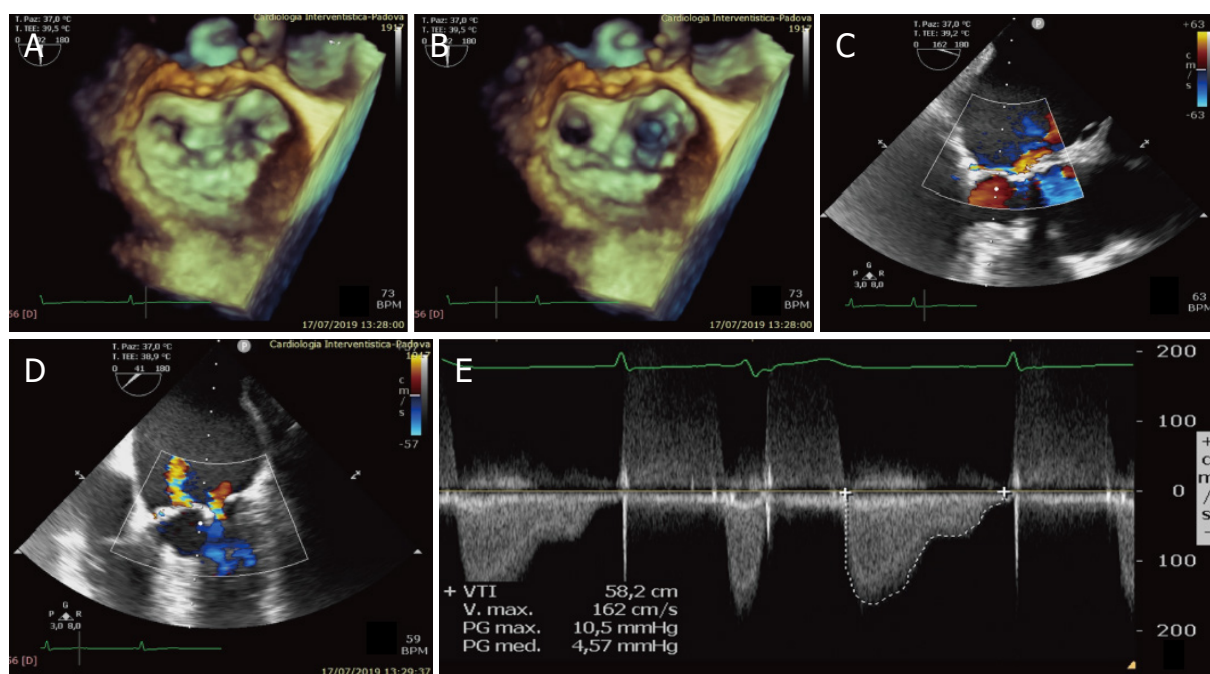


Figure 7. Final result. The 3D TEE shows the new "double orifice" mitral valve (A, B) with mild residual mitral regurgitation (C, D); continuous doppler (E) shows a final transvalvular gradient less than 5 mmHg

The patient was discharged after 3 days without peri-procedural complications. After 30 days, a follow-up transthoracic echocardiogram showed mild MR and stable transvalvular gradients. One year later the patient confirmed a clinical status improvement (NYHA functional class I-II) with no further hospital admissions for heart failure.

DECLARATIONS

Authors' contributions

Participated to the conception and the drafting of the manuscript, its critical revision for important intellectual content and the final approval of the submitted text; agreed for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Rodinò G, Masiero G, Tarantini G

Availability of data and materials

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Conflicts of interest

Tarantini G reports honoraria for lectures from Abbott Vascular and Edwards Lifesciences; Rodinò G and Masiero G declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Percutaneous “edge-to-edge” leaflet repair in patients with secondary mitral valve regurgitation

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Abstract

Functional or secondary mitral regurgitation (MR) is a heterogeneous entity afflicting patients with heart failure both with reduced or preserved left ventricular ejection fraction. It results from an imbalance between closing forces and tethering or pushing strengths acting on the valve in the absence of structural alterations of mitral valve (MV) apparatus. According to previous studies, more than 20% of patients with heart failure and reduced left ventricular ejection fraction have severe MR, even though the definition of the severity of the MV disease in this setting remains a debated issue due to the poor reproducibility of quantitative measurements and its dynamic nature, highly dependent on left ventricular loading conditions and performance in relation to optimization of medical treatment. Furthermore, it is still unclear whether MR is a direct contributor to a worse prognosis or merely a marker of severity of the disease affecting the left ventricle. Isolated MV surgery in these patients is burdened by significant operative mortality, high rates of recurrent MR and absence of proven survival benefit. In recent years, percutaneous treatment of functional MR arose as a viable and safe alternative to conventional surgery, proving capable of reducing symptoms and recurrent hospitalization rates for heart failure, and even improving prognosis in selected patients. In this review we will discuss the percutaneous treatment of functional MR through transcatheter “edge-to-edge” leaflet repair performed with the two systems currently available: the MitraClip System and the PASCAL Repair System, from available evidence to technical practice.

Keywords: Functional mitral valve disease, mitral regurgitation, mitral insufficiency, heart failure, MitraClip, PASCAL



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INTRODUCTION

Secondary mitral valve regurgitation (MR) is a heterogeneous entity afflicting patients with heart failure (HF) and is almost twice as common as the degenerative type. It occurs in up to 60% of patients after a myocardial infarction and is present in more than half of patients with dilated cardiomyopathy^[1]. Despite its high prevalence, the optimal therapeutic approach remains a matter of debate, with a disappointingly low level of evidence for guideline recommendations. The aim of this review is to portray the percutaneous treatment of functional MR through transcatheter “edge-to-edge” leaflet repair, from available evidence to technical practice.

ETIOLOGY AND TREATMENT OF SECONDARY MR

Functional MR results from an imbalance between closing forces and tethering or pushing strengths acting on the valve in the absence of structural alterations of mitral valve (MV) apparatus. It may occur in patients with heart failure both with reduced ejection fraction (HFrEF) or with preserved ejection fraction (HFpEF)^[2]. In the former setting, the underlying ischemic or non-ischemic triggers determine an eccentric left ventricle (LV) remodeling, either global or regional, with papillary muscle displacement resulting in enhanced tethering forces on the leaflets; on the other hand, ventricular dysfunction and annular dilatation determine a reduction in closing forces. The resulting secondary MR turns in chronic LV volume overload, thus inducing further remodeling and progression of the disease. In time, an LV diastolic dysfunction occurs, causing an increase in left atrial (LA) pressure and subsequent LA remodeling and enlargement with further annular dilatation, thus contributing to MV tenting^[2,3] [Figure 1]. More than 20% of patients with HFrEF have severe MR, with comparable rates between ischemic and non-ischemic etiologies^[4]. Functional MR is also found in a significant proportion of patients with HFpEF but still little is known about its pathogenesis, clinical implications, and prognostic importance. Clinical conditions frequently associated in this setting include atrial fibrillation, severe aortic stenosis, diabetes mellitus and myocardial ischemic disease. Systolic MV tenting is supposedly due to LV diastolic dysfunction causing increased LV and LA filling pressure, which in turn determines LA enlargement, annular dilatation, and leaflets malcoaptation^[2,3] [Figure 1]. Given the lack of data on prognosis, therapeutic options and management algorithms of MR in this clinical setting, this review will focus on the percutaneous treatment of MR in patients with HFrEF. In this setting, independent of the etiology of HFrEF, a higher degree of mitral regurgitation is strongly associated with poor clinical outcomes, even though it remains uncertain if it is a direct contributor to a worse prognosis or merely a marker of severity of the disease affecting the LV^[5-7]. As a matter of fact, current European guidelines set lower thresholds for effective regurgitation orifice area (EROA) and regurgitant volume (RVol) to define severe secondary MR ($\text{EROA} \geq 20 \text{ mm}^2$; $\text{RVol} \geq 30 \text{ mL}$) compared to that used for primary MR ($\text{EROA} \geq 40 \text{ mm}^2$; $\text{RVol} \geq 60 \text{ mL}$)^[1,8,9]. However, the definition of the severity of MV disease remains a debated issue due to the poor reproducibility of EROA measurements, the close dependence of the EROA and RVol values on LV volume, and lastly, the dynamic change of LV loading conditions and performance after optimization of medical treatment^[1,8,10-12] [Table 1]. Therefore, a careful integration of quantitative, semiquantitative and qualitative echocardiographic parameters and clinical data, is necessary for deciding appropriate treatment. Different from primary MR, there is no evidence that surgical correction of valvular disease improves survival. Therefore, surgery is recommended only for patients with symptomatic severe MR and a left ventricular ejection fraction (LVEF) $> 30\%$ undergoing coronary artery by-pass graft, or in patients with lower EF but with evidence of myocardial viability and an option for revascularization. Isolated MV surgery is burdened by significant operative mortality, high rates of recurrent MR, absence of proven survival benefit and it may be considered in low surgical risk patients remaining symptomatic despite optimal medical management, including cardiac resynchronization therapy (CRT) with no markedly reduced LV function^[1]. In cases of suitable valve morphology, transcatheter treatment remains an opportunity for higher surgical risk patients or for those without a revascularization option, after careful Heart-Team evaluation. Based on current clinical guidelines, transcatheter repair of

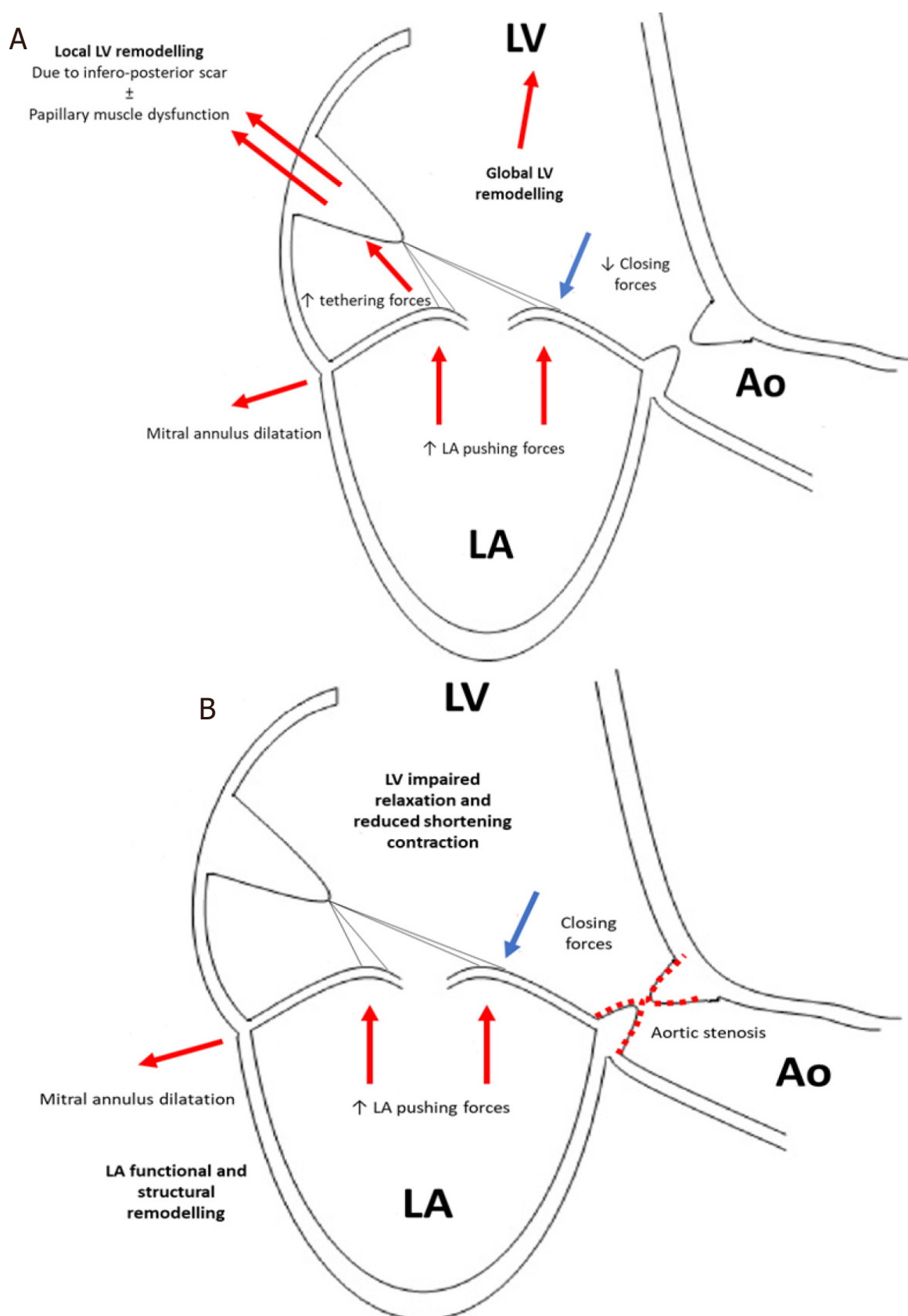


Figure 1. Underlying mechanisms of functional MR in HFrEF (A) and HFpEF (B). In HFpEF aortic stenosis may be one of the underlying conditions causing LV impaired relaxation and reduced shortening contraction. Other frequent conditions are diabetes mellitus and myocardial ischemic disease. Another possible condition is atrial fibrillation which, instead, directly causes LA functional and structural remodelling. MR: mitral regurgitation; LA: left atrium; LV: left ventricle; Ao: aorta

Table 1. Association between MR severity and prognosis in real-world registries

Author	No. of pts.	Type of study	LVEF cut-off	Etiology of MR	Method of grading MR	MR as independent predictor of mortality
Grigioni <i>et al.</i> ^[6]	303	Single center, Observational	N/A	Ischemic (post-MI)	QD, PISA	EROA ≥ 20 mm ²
Lancellotti <i>et al.</i> ^[7]	98	Single center, Observational	< 45%	Ischemic	PISA	EROA ≥ 20 mm ²
Rossi <i>et al.</i> ^[5]	1,256	Multicenter, Observational	N/A	FMR 62% ischemic	VCW, PISA	EROA ≥ 20 mm ² VCW > 0.4 cm
Patel <i>et al.</i> ^[10]	558	Single center, Observational	< 35%	FMR 54% ischemic	PISA	No difference for EROA \geq or < 20 mm ²
Grayburn <i>et al.</i> ^[11]	336	Substudy of multicenter RCT	< 35%	FMR 57% ischemic	VCW, QD, PISA	MR not a predictor; VCW \geq 0.4 cm only for a composite EP

Pts.: patients; LVEF: left ventricular ejection fraction; N/A: not available; QD: quantitative Doppler; PISA: proximal isovelocity surface area; VCW: vena contracta width; EROA: effective regurgitant orifice area; RCT: randomized clinical trial; EP: endpoint; MR: mitral regurgitation

the MV may be considered as a second or third-line therapy in symptomatic (New-York Heart Association functional class ≥ 2) patients with HFrEF and one of the following^[1,9]:

- (1) Severe functional MR despite maximum tolerated medical therapy, with no indication to CRT or heart transplant/left ventricular assist device (HT/LVAD) and high surgical risk due to old age, frailty, or severe comorbidity.
- (2) Severe MV disease despite optimal medical therapy and non-responder to CRT, with high surgical risk and no indication to HT/LVAD.
- (3) Severe secondary MR despite maximum tolerated medical therapy, non-responder to CRT and with an indication to HT, as a “bridge therapy”.

The MitraClip System (Abbott Vascular, Santa Clara, CA, USA) is the most investigated and adopted device for percutaneous “edge-to-edge” valve repair in functional MV disease. Despite being less effective than conventional surgery in reducing MR, it has achieved higher safety, similar improvements in clinical outcomes and a survival benefit compared to medical therapy, as recent studies have shown^[13-15]. However, the conflicting results of the latest two major trials investigating the use of MitraClip in secondary MR highlighted a great debate on optimal patient selection criteria for this procedure^[14,15]. Adjunctively, the new PASCAL repair system (Edwards Lifesciences, Irvine, CA, USA) recently received CE-mark for the treatment of functional and degenerative MR [Figure 2].

TECHNICAL ASPECTS OF THE TRANSCATHETER MV “EDGE-TO-EDGE” LEAFLET REPAIR FOR THE TREATMENT OF FUNCTIONAL MR

Patient selection for the percutaneous “edge-to-edge” procedure is currently performed by pre-operative multi-modality imaging assessment, using both 2D and 3D transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). TEE allows for confirmation and severity assessment of secondary MR, as well as evaluation of the anatomic suitability for a MitraClip implantation. Currently, the main exclusion criteria include a very short posterior leaflet (< 7 mm), a mitral valve area < 3 cm², the presence of severe calcification of the leaflets in the grasping area and a combined MV disease on rheumatic basis. As stated before, since MR is a dynamic condition, it is necessary to perform the pre-operative evaluation in the best hemodynamic conditions possible, with normal blood pressure and heart rate following optimization of medical therapy.

In the last decade, thousands of patients treated with the MitraClip System achieved significant improvements in symptoms, functional status and quality of life, favorable LV remodeling and a reduction of HF hospitalizations^[13,16]. This device reproduced the surgical “edge-to-edge” repair of the MV through a

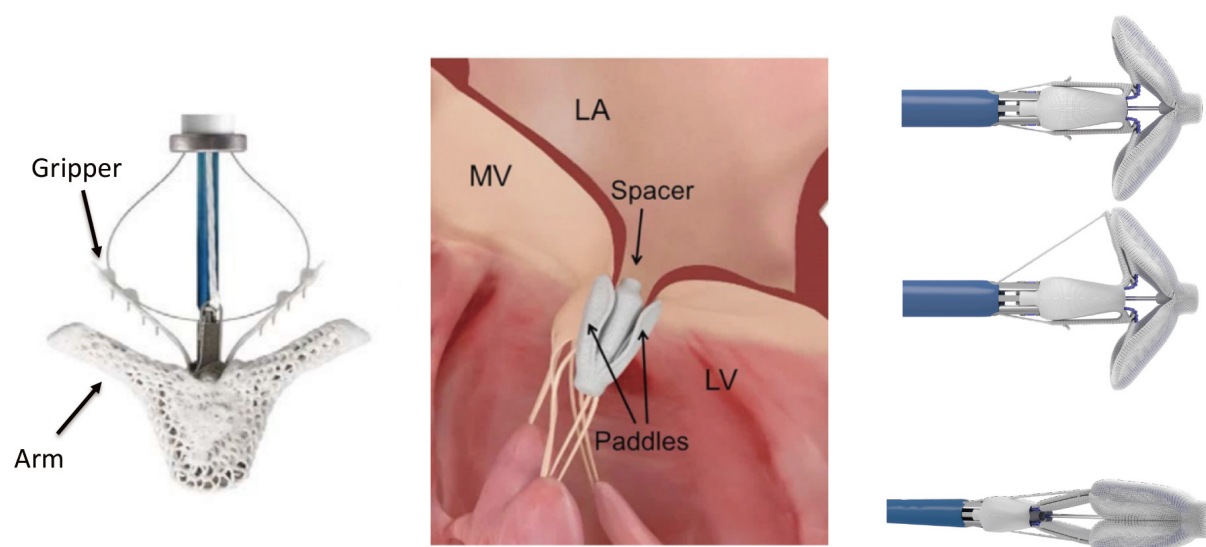


Figure 2. The PASCAL implant consists of a 10 mm central nitinol woven spacer that acts as a filler in the regurgitant orifice of the MV, and in its closed conformation is attached to the valve leaflets by two paddles and clasps. Differently from the MitraClip system, each of the 2 clasps can be activated independently and the device can take an elongated form. LA: left atrium; LV: left ventricle; MV: mitral valve

percutaneous approach, producing a “double-orifice” valve and reducing the severity of the regurgitation. The steerable 24 Fr catheter with a clip delivery system on its proximal end clip is advanced in the LA through a transseptal approach using a venous femoral access, and then further advanced in the LV to effectively grasp together the MV leaflets. The whole procedure is carried out under general anesthesia and with fluoroscopic and TEE imaging guidance. As opposed to the MitraClip system, the PASCAL implant consists of a 10 mm central nitinol woven spacer that acts as a filler in the regurgitant orifice of the MV, and in its closed conformation is attached to the valve leaflets by two paddles and clasps [Figure 2]. The paddles, which rest on the ventricular side of the valve leaflets, secure the leaflets against the nitinol spacer and ensure a low and homogeneous pressure distribution on the valve tissue. Furthermore, the paddles flex on every heart beat so that the system dynamically flexes as the valve opens and closes, preserving the native anatomical geometry. Using the PASCAL system, each of the 2 clasps can be activated independently, so that tissue insertion between the paddles and the spacer can be optimized, improving results, allowing distribution of the traction on valve leaflets while maintaining a larger mitral orifice. Furthermore, low mitral gradients are ensured even in the case that two devices are needed. The PASCAL system consists of a steerable guide sheath intended to provide height on the mitral annulus plane, a steerable catheter allowing access to different locations across the coaptation line and an implant catheter that extends from the left atrium into the LV, used to deliver the implant. The three independent catheter movements in all planes allow for an easy height compensation in cases of sub-optimal trans-septal crossing, an intuitive control of the delivery system and a very simple positioning and orientation of the implant. Therefore, it is intended to assist the operator in the treatment of challenging anatomies, such as short posterior leaflets, large flail gaps, severe tethering, and severe annular dilatation. However, further studies are needed to assess the safety and effectiveness of this novel device in this complex anatomical setting.

Standard medical treatment to prevent clinically relevant stroke after percutaneous edge-to-edge MV repair is still a debated issue, due to the lack of dedicated randomized clinical trials aimed at comparing different treatment strategies. In the EVEREST II trial, patients were treated with heparin during the procedure, and a combination of aspirin (at a dose of 325 mg daily) for 6 months and clopidogrel (at a dose of 75 mg daily) for 30 days after the procedure^[16]. Therefore, in the absence of risk factors requiring antithrombotic therapy such as atrial fibrillation, dual antiplatelet therapy using aspirin and clopidogrel for up to 6 months

is currently the preferred therapeutic strategy^[17]. However, recent observational studies suggest that temporary oral anticoagulation, with coumadin or apixaban, might be an effective strategy to reduce the incidence of stroke within the first 30 days after the MitraClip procedure in patients with maintained sinus rhythm, without an increase in minor and major bleeding events^[18,19]. Adjunctive data relevant to medical treatment after a PASCAL implantation procedure are inadequate. Further studies should be conducted to address this important issue.

EVIDENCE ON PERCUTANEOUS “EDGE-TO-EDGE” LEAFLET TREATMENT IN SECONDARY MR

Data on safety and effectiveness of the MitraClip device for the treatment of functional MR mainly result from two real-world prospective European multicenter registries and the two latest major trials^[14,15,20,21].

The ACCESS-EU study enrolled a total of 567 elderly patients with significant MR between 2009 and 2011, of which 79% presented with secondary MR, 85% with NYHA class III or IV, and 53% with LVEF \leq 40%. Acute procedural success occurred in 99.6% of patients. The survival rate at 1-year follow-up was 82% with low rate of subjects (6%) requiring MV surgery. Moreover, there was significant clinical improvement, with durable residual MR $< 2+$ and NYHA class I/II in the majority of patients (respectively 79% and 71%) with a higher six-minute-walking-test and Minnesota-living-with-heart-failure score performance^[20].

In the following two years, the SENTINEL registry enrolled 628 patients with a mean age of 74 ± 10 years, lower than that of the ACCESS-EU study. Once again, functional MR was the prevalent pathogenesis (72%). Acute procedural success was high (95%) with only one clip implanted in two thirds of the population. The 1-year mortality was comparable to previous studies (15%), with a significantly higher rate of rehospitalization compared to the degenerative group (26% vs. 12%, $P = 0.009$). Echocardiographic follow-up data showed a persistent reduction in the degree of mitral regurgitation at 1 year, with 6.0% of patients with residual severe MR^[21].

More recently, two large randomized clinical trials compared the MitraClip procedure to conservative treatment^[14,15]. Despite their similarities, the studies showed conflicting results and conclusions, fostering the debate about the potential association between this transcatheter mitral repair and a significant survival benefit. Both MITRA-FR and COAPT were multicenter, randomized, open-label trials that enrolled 304 and 614 high surgical risk patients with HFrEF and symptomatic moderate-to-severe or severe functional MR respectively, with comparable rates of ischemic and non-ischemic etiologies. However, different from the first study, the latter involved higher volume centers and greater performance, performed a more rigorous clinical and instrumental patient selection, and proved a more careful medical therapy up-titration. At 12 months follow-up, the rate of the primary outcome (death from any cause or unplanned hospitalization for HF) was comparable between the two treatment groups of the MITRA-FR (55% in the interventional group vs. 51% in the control group, $P = 0.53$) with no significative difference among the individual components of the composite endpoint^[14]. Conversely, the primary outcome in the COAPT trial consisted of all hospitalizations for HF within 24 months of follow-up, showing a significantly lower annualized rate in the device group as compared with the control group (respectively, 36% per patient-year vs. 68% per patient-year, $P < 0.001$). Moreover, the secondary endpoint of death from any cause within 24 months occurred in 29% of the patients in the MitraClip group as compared with 46% in the conservative group ($P < 0.001$). These clinical improvements and benefits were consistent across numerous subgroups, including patients who had ischemic MR etiology and non-ischemic cardiomyopathy, and were independent of the MR grade and LV volume and function at baseline^[15]. Therefore, several authors highlighted that the studies indeed enrolled 2 distinctly different groups of patients; as a matter of fact, the patients enrolled in the COAPT trial had an almost 30% higher mean EROA with an approximately 30%

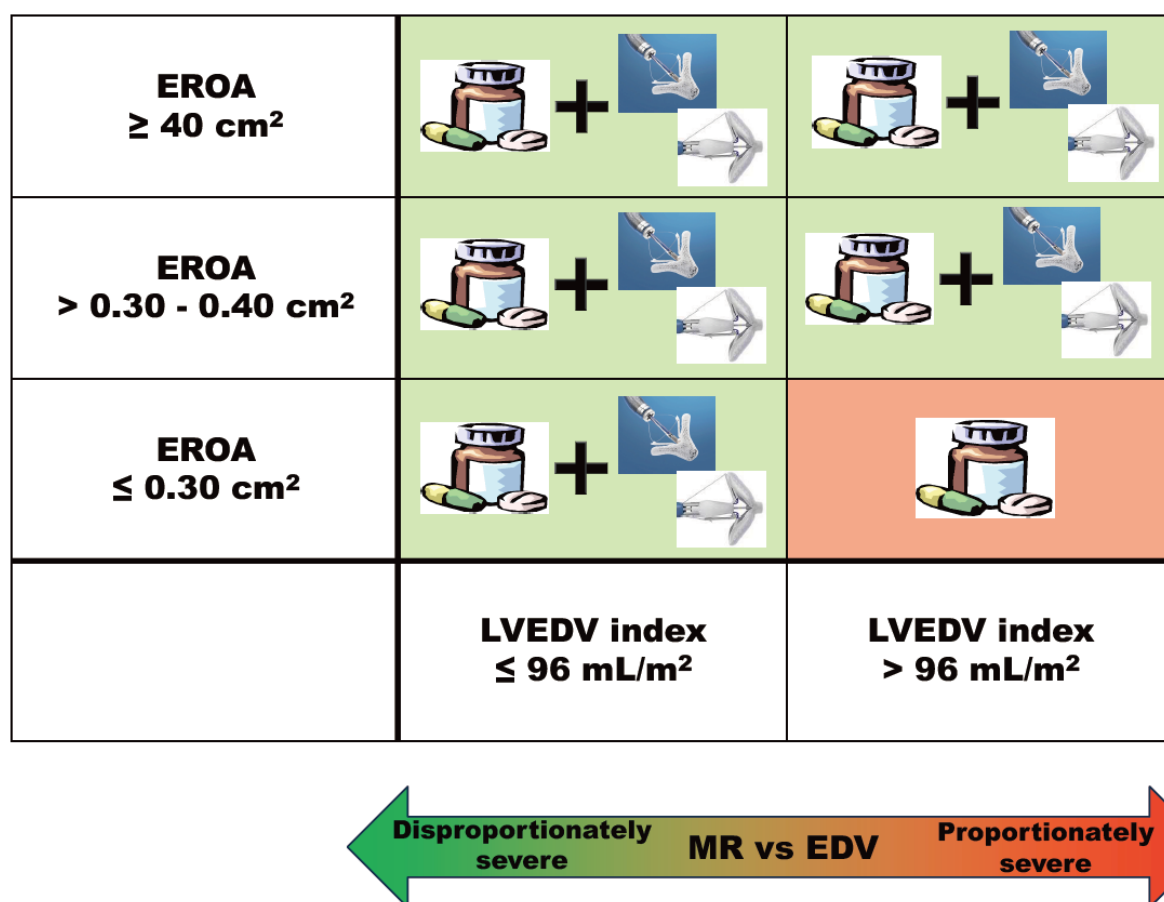


Figure 3. Treatment option (OMT, TMVR) of functional MR in patients with disproportionate or proportionate severe MR according to EROA and LVEDV. Based on an analysis of subgroups of patients enrolled in the COAPT trial and the MITRA-FR trial by M. Packer and P.A. Grayburn^[26]. EROA: effective regurgitant orifice area; LVEDV: left ventricular end-diastolic volume; MR: mitral regurgitation; TMVR: transcatheter mitral valve repair; OMT: optical medical therapy. Copyright of the figure belongs to Prof. Tarantini

smaller average LVEDV as compared with those in the MITRA-FR trial. Furthermore, by stratifying the COAPT study population according to the level of EROA, only those patients with an EROA $< 30 \text{ mm}^2$ in the setting of a dilated LV ($> 96 \text{ mL/m}^2$) did not benefit from the MitraClip procedure. It has been speculated that the survival benefit shown in the COAPT study was strictly dependent on the selection of patients with a greater degree of MR, disproportionately higher than the amount of LV enlargement, and the exclusion of those with a more advanced stage of LV disease [Figure 3]^[22]. Further data on the treatment of functional MR in HFrEF patients with the MitraClip System will be provided by two ongoing RCTs: the Reshape-HF2 trial (NCT02444338) and the MATTERHORN trial (NCT02371512).

Current evidence about the PASCAL device is limited to the multicenter CLASP CE-Mark study, a prospective, single-arm study involving 62 patients with moderate-to-severe or severe MR and up to 52% with functional etiology^[23-25]. Preliminary data showed encouraging results with a 95% successful implantation rate, low major adverse event rate at 30 days, and sustained clinical improvement at 6-month and 1-year follow-ups in terms of MR grade reduction, NYHA functional class, 6-minute walk distance and Kansas City Cardiomyopathy Questionnaire and EQ-5D scores gain. Further data will be provided by the Edwards PASCAL CLASP IID/IIF Pivotal Clinical Trial (CLASP IID/IIF; NCT03706833), a prospective, multicenter, randomized, controlled trial comparing this novel device to the MitraClip.

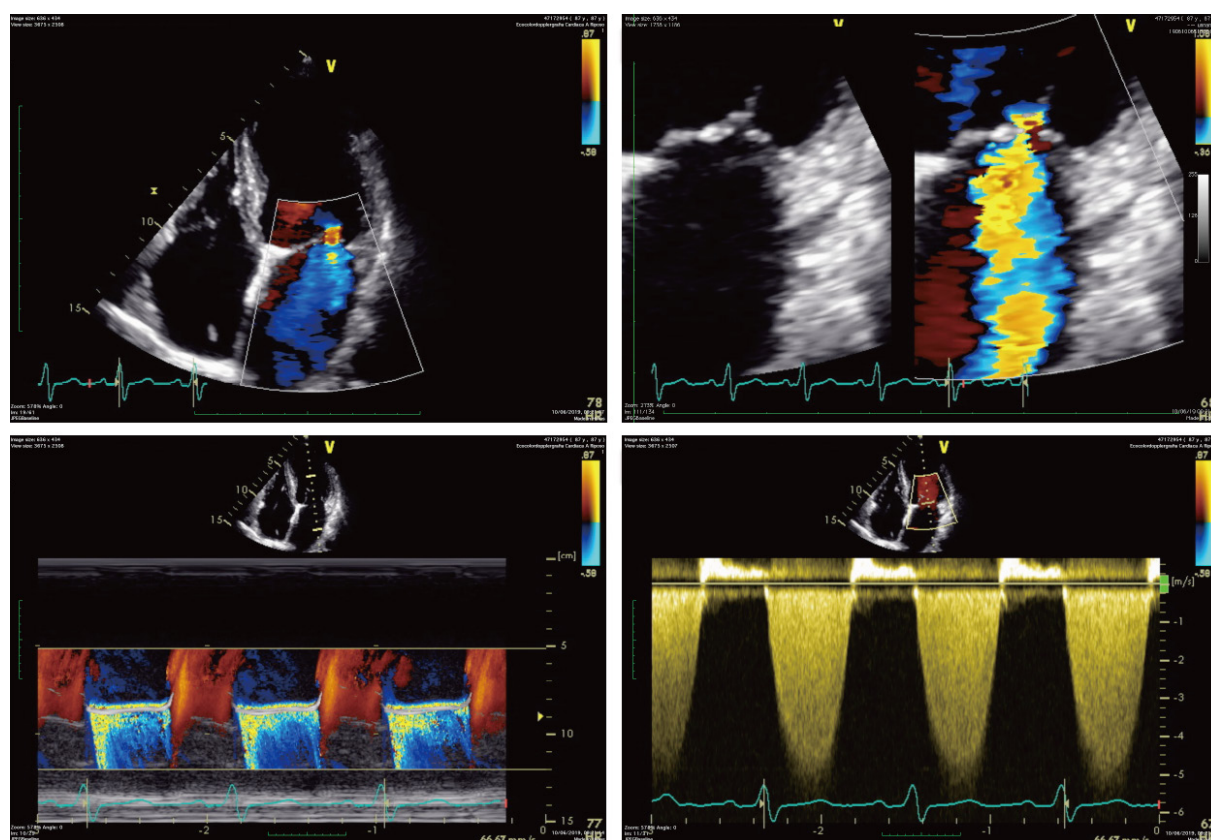


Figure 4. Pre-procedural transthoracic Doppler echocardiography evaluation of the mitral valve showing severe functional mitral regurgitation with a holosystolic central jet in a dilated cardiomyopathy (in particular: posterior leaflet of 8 mm, an effective orifice area of 30 mm² and a mitral valve area of 5 cm²)

CASE EXAMPLE: SECONDARY MR TREATED WITH THE PASCAL SYSTEM

We report a case of an 88-year-old male with a history of ischemic cardiopathy already treated with percutaneous coronary intervention on left anterior descending coronary artery and right coronary artery, previous pace-maker implantation, severe chronic nephropathy and obstructive pulmonary disease. He progressively developed a severe functional MR with NYHA functional class II-III despite optimal medical therapy; a CRT therapy was not indicated and the previous stents on LAD and RCA were well working at the follow-up coronary angiography. The MV disease severity was evaluated on the basis of and confirmed by TEE. The 2D and 3D TTE showed a moderate reduction of the LVEF, regional wall motion abnormalities and preserved ventricular dimension, a normal right ventricular systolic function with mild pulmonary hypertension, a severe LA dilatation and a severe functional MR with a holosystolic central jet due to the tethering of a short posterior leaflet (8 mm), an effective orifice area of 30 mm² and a MV area of 5 cm² [Figure 4]. Given the advanced age and frailty, after the TEE assessment, a multidisciplinary Heart-Team defined the patient a suitable candidate for percutaneous “edge-to-edge” repair with the PASCAL repair system. The major MR jet was across A2-P2 segment so the intended implantation strategy was one central PASCAL device. A trans-septal puncture was done, aiming for a posterosuperior position in the fossa ovalis and with a measured height of 4.0-4.5 cm over the atrio-ventricular plan. Under TEE and fluoroscopic guidance, the steerable guide sheath and the steerable catheter were introduced into the LA while simultaneously flexing the implant catheter towards the MV. The valve was crossed with the opened paddles, achieving a straightforward position below the leaflets. After the 3D-TEE orthogonal alignment to the coaptation mitral line [Video 1], the implant was retracted until the leaflets were grasped simultaneously and thereafter optimized independently to place the leaflet deeper and its tip closer to the spacer

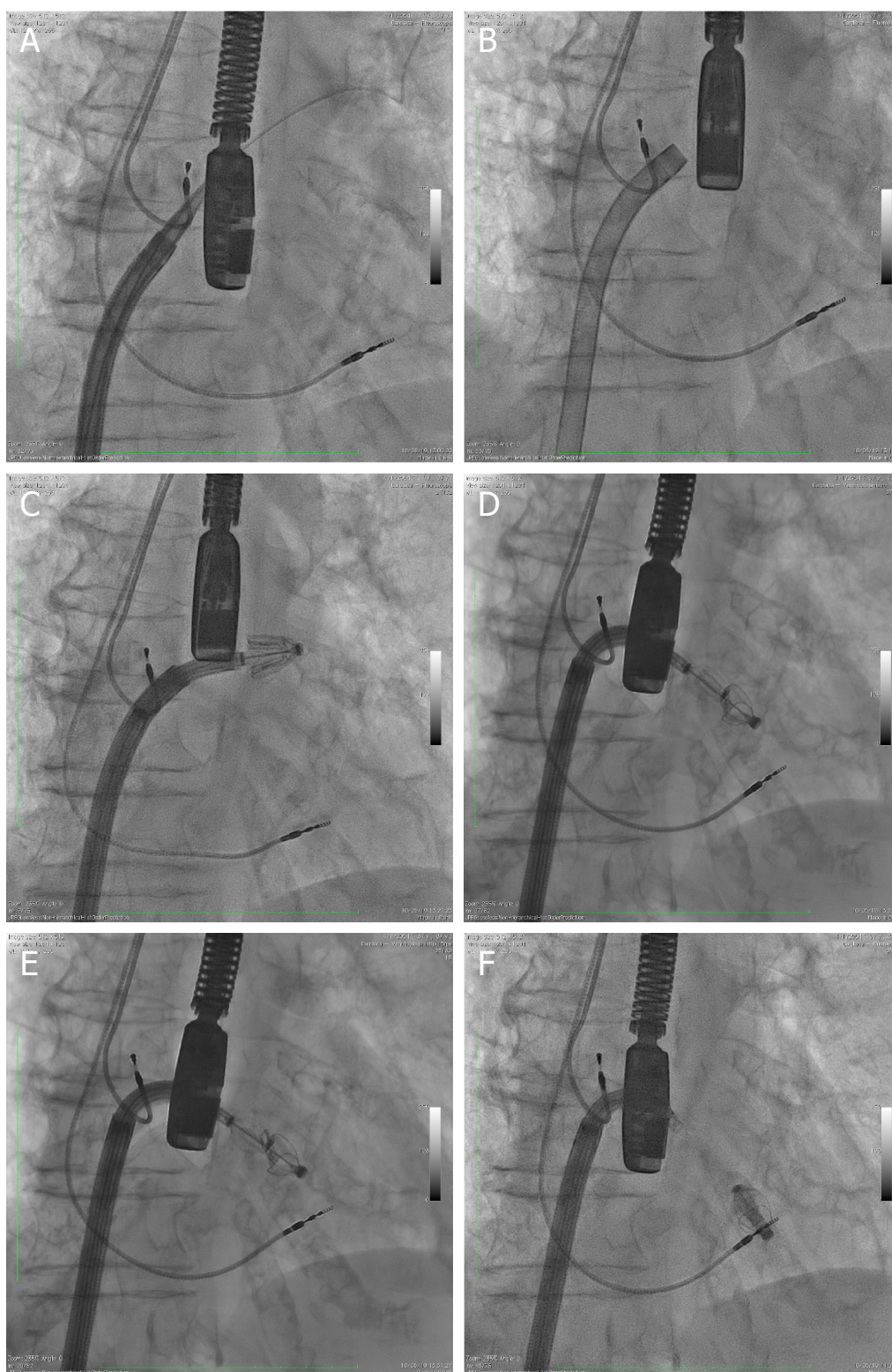


Figure 5. Procedural fluoroscopic steps for the implantation of the Edwards PASCAL transcatheter mitral valve repair system. With a transeptal approach, the steerable guide sheath and the steerable catheter were introduced into the left atrium while simultaneously flexing the implant catheter toward the mitral valve (A-C); the valve was crossed with the opened paddles achieving a straightforward positioning below the leaflets. After the three-dimensional transesophageal echocardiography guided orthogonal alignment to the coaptation mitral line, the implant was retracted until leaflets were grasped simultaneously (D, E); when sufficient and straight leaflet insertion was confirmed, the clamps were dropped, and device was closed. Immediately after, the residual mitral regurgitation and transvalvular gradient were systematically assessed to confirm optimal mitral regurgitation reduction before final deployment (F)

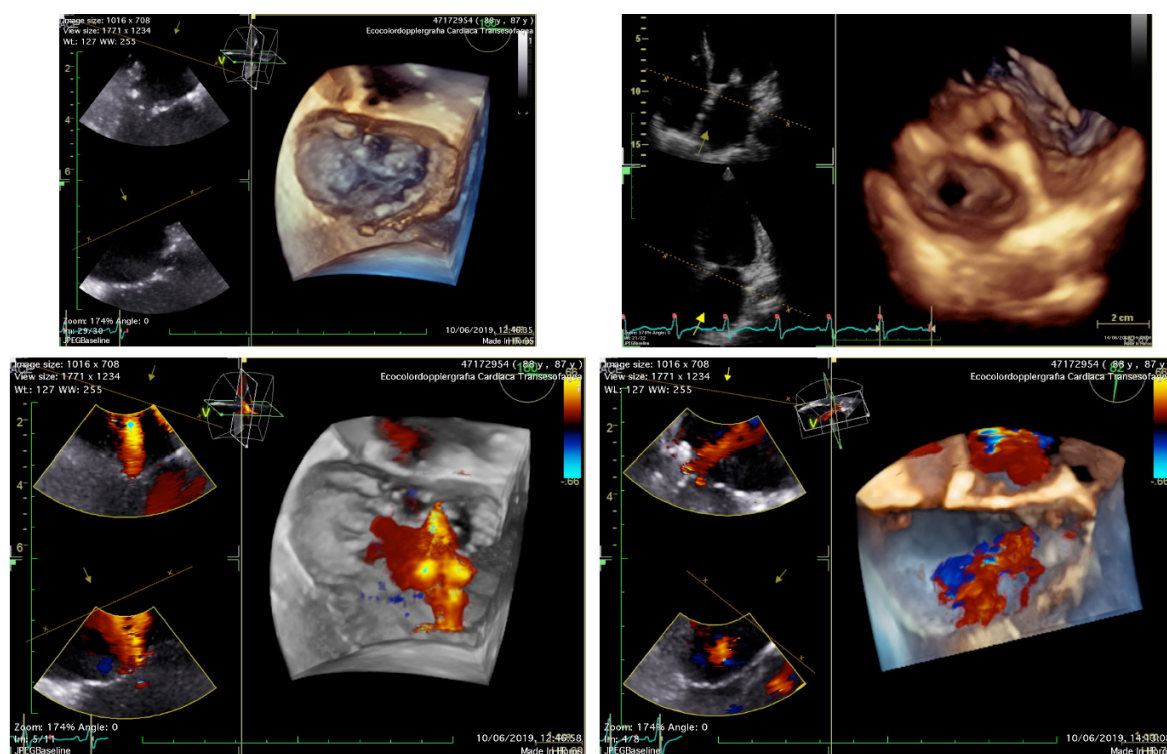


Figure 6. Periprocedural three-dimensional transesophageal echocardiography evaluation of mitral valve showing a pre-procedural severe functional mitral regurgitation with a holosystolic central jet and a consistent post-procedural reduction of the mitral regurgitation grade with the typical “double-orifice” valve

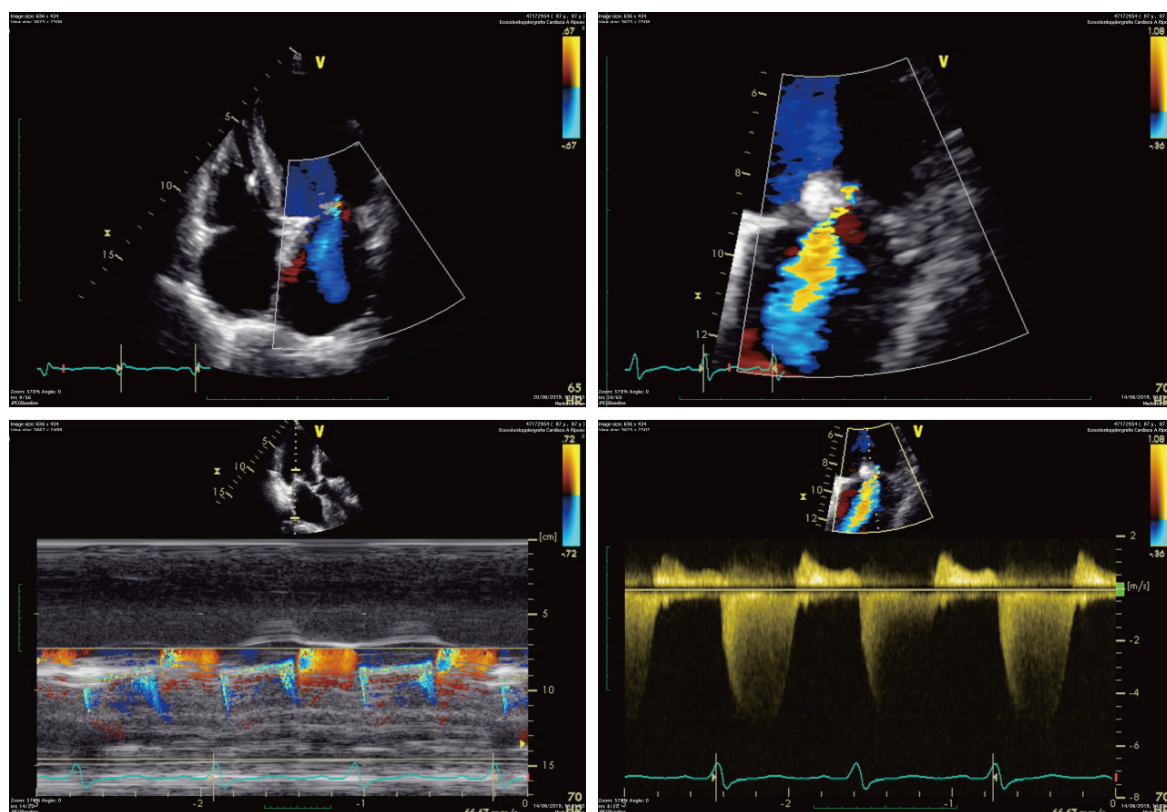


Figure 7. Post-procedural transthoracic Doppler echocardiography mitral valve evaluation showing mild regurgitation with acceptable mitral gradient (in particular: mean MV gradient of 3 mmHg, an effective orifice area of 14 mm² and a MV area of 3 cm²)

[Videos 2 and 3]. When sufficient and straight leaflet insertion was confirmed, the clasps were dropped, and device was closed. Immediately after, the residual MR and transvalvular gradient were systematically assessed to confirm optimal MR reduction before final deployment [Figures 5 and 6] [Video 4]. Remarkably, a drop in the mean left-atrial pressure from 16 to 8 mmHg was observed. Mild regurgitation was confirmed at TTE before discharge (in particular: residual mean MV gradient of 3 mmHg, effective orifice area of 14 mm² and MV area of 3 cm²) [Figure 7] and at 30-days follow-up with acceptable mitral gradient and clinical improvement (NYHA class I-II).

CONCLUSION

The percutaneous treatment of functional MR through transcatheter “edge-to-edge” leaflet repair has recently risen as a viable and safe alternative to conventional surgery in selected patients with severe disease who remain symptomatic despite maximally tolerated guideline-directed medical therapy and judged at high surgical risk by a multidisciplinary and experienced heart team. Two devices are currently available, the MitraClip and the PASCAL Repair Systems, with peculiar technical aspects and evidence.

DECLARATIONS

Authors' contributions

Participated to the conception and the drafting of the manuscript, its critical revision for important intellectual content and the final approval of the submitted text; agreement for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Masiero G, Rodinò G, Tarantini G

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Tarantini G reports honoraria for lectures from Abbott Vascular and Edwards Lifesciences; Masiero G and Rodinò G declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

Open Access



Robotic pancreaticoduodenectomy and splenopancreatectomy: technical aspects and review of literature

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Abstract

Robotic pancreatic surgery provides several advantages. Since the first report of a robotic-assisted distal pancreatectomy in 2001, total pancreatectomies, pancreatic tumor enucleations, pancreaticoduodenectomy, central pancreatectomy and Appleby procedures have been performed, indicating a promising future. The aim of this article is to describe our experience of robotic pancreatic surgery including technical aspects for pancreaticoduodenectomy and distal pancreatectomy. The current literature on feasibility, safety and early postoperative outcomes will be discussed.

Keywords: Robotic, pancreatectomy, distal, duodenopancreatectomy, Whipple

INTRODUCTION

Morbidity and mortality associated with pancreatic surgery has decreased over the last decades because of advances in anesthesia, critical care and other aspects of perioperative management. Improvement in surgical technique and instrumentation as well as centralization of care to high-volume pancreatic surgery centers has significantly contributed to improvement in postoperative short- and long-term outcomes^[1].



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The robotic platform provides significant dexterity-related advantages, enabling pancreatic procedures to be performed with surgeon- and patient-related benefits. Complex demanding procedures such as pancreaticoduodenectomies (PDs) involving dissection of the hepatoduodenal ligament and resection of the pancreatic head, uncinate process and duodenum, followed by a complex reconstruction with delicate anastomoses become technically feasible using a minimally invasive approach^[2]. Adjuncts such as built-in fluorescence imaging FireFlyTM and TileProTM picture overlay while performing intraoperative ultrasound add to operative safety and efficiency. At our high-volume center, we have performed more than 180 robotic PDs since 2012 and over 200 distal pancreatectomies with splenectomy (DPS) since 2008. We have found lower complication rates for robotic PD along with no differences in total costs when compared with the open PD, but more importantly, robotic PD may offer improved oncologic outcomes^[3,4].

When starting a robotic program for pancreatic surgery, a dedicated team with prior experience in open as well as minimally invasive pancreatic surgery and, first and foremost, a structured training is the key to success^[5]. During the early stages of the learning curve, proficiency in DPS should be achieved^[6]. However, learning curves can be considerably diminished by appropriate training, proficient mentorship and an experienced multidisciplinary team^[7-9].

The aim of this article is to describe the technical aspects of robotic PD and DPS. Our own expertise as well as the current literature on feasibility, safety and early postoperative outcomes will be discussed.

TECHNIQUE OF ROBOTIC PANCREATIC SURGERY (XITM SYSTEM)

Patient selection

Patient selection plays a crucial role during the early learning curve for successful robotic pancreatic surgery. Patients with a very high or very low body mass index ($BMI > 40 \text{ kg/m}^2$; $BMI < 17 \text{ kg/m}^2$), petite body habitus and relevant comorbidities, elderly frail patients and those with multiple previous abdominal surgeries should be evaluated thoroughly^[10]. Patients with chronic pancreatitis, neuroendocrine tumors, cystic neoplasms, ampullary cancers and distal cholangiocarcinomas may be considered as ideal PD candidates for surgeons with juvenile robotic experience. Tumor entity, location and extent are important factors in determining whether a robotic approach is beneficial for the patient. Borderline resectable pancreatic tumors may require concomitant vascular or multi visceral resection demand for robotic expertise as well as master skills and should be avoided during the learning curve. A recent NSQIP database study comparing early postoperative outcomes for patients undergoing laparoscopic or robotic PD reported higher overall complications and conversion rates for the robotic approach if the procedure is combined with vascular or multivisceral resection^[10].

Equipment and preoperative measures

As for robotic pancreas procedures using the Xi system, we recommend the use of PrograspTM forceps, fenestrated bipolar and mono-polar scissors as well. The robotic vessel sealerTM is the key device in facilitating dissection while achieving adequate hemostasis. Fortunately, a new sealing device with a more delicate articulating tip and shorter seal time is soon to be launched (SynchroSealTM). Locking robotic plastic clips (HemolokTM, WeckTM) are used prior to the division of larger vessels. Pancreatic transection may be achieved with the help of the robotic stapler. Cutting or non-cutting needle drivers may be used for reconstruction according to surgeon's preference. A commonly used suture for our robotic pancreatic procedures is 4-0 or 5-0 Monocryl [Table 1].

Most surgical departments have designated robotic operating suites. Placement of the robotic cart, console(s), and audio/video towers in relation to the patient, scrub team and anesthesia is set up according to the surgeon's preferences ahead of surgery. The patient table is placed at 45 degrees to the anesthesia team. Both arms are abducted, and the patient is positioned supine with slight flexion and slight reverse Trendelenburg. The robot cart docks from the right of the patient table.

Table 1. Equipment for robotic pancreatic procedures

Items	Details (number)
Robotic system	Da Vinci TM Xi
Robotic instruments	30-degree camera Prograsp TM Fenestrated Bipolar Mono-polar scissors Large and diamond needle drivers Bipolar vessel sealing device Large clip applier Robotic bulldog clamps Ultrasound probe
Ports	12 mm assistant trocars (4) 8 mm robotic trocars
Basic laparoscopic tray	Veress needle Suction - irrigation Needle drivers Stapling devices on standby
Suture	0 Vicryl suture 4-0 V-lock 4-0 Monocryl, cut to 20/15/12 cm 5-0 Monocryl, cut to 12 cm 6-0 Monocryl, cut to 12 cm
Specimen bags	Cook LapSac TM - 5 × 8, 8 × 10 (inches)
Drains	19 French Blake drain

Entry and port placement

Access is obtained by an infraumbilical incision and abdominal insufflation via a Veress needle followed by a 12-mm bladeless trocar insertion. In patients with previous surgery, insufflation may be obtained by placing a Veress needle in the left subcostal region in the mid clavicular line followed by entry with a 5-mm bladeless trocar and 5-mm laparoscope.

Using the Xi system, the 12-mm umbilical port is used as the assistant port. This may also serve as a robotic working port (robotic stapler). The robotic ports are placed along a straight line at variable distance from target anatomy depending on the patient's body habitus. The robotic camera trocar is placed in the right mid-clavicular line. Two working ports are placed on the left, with one on the right at distance of 6-8 cm between each port [Figure 1A (DPS) and B (PD)]. When using the robotic stapler, the 12-mm robotic trocar is inserted at the site of the assistant port followed by bringing down arm number 3.

DISTAL PANCREATECTOMY AND SPLENECTOMY

ProGraspTM and fenestrated bipolar forceps are used to enter the lesser sac. The robotic vessel sealer is used to divide the gastrocolic and splenocolic ligament. Congenital adhesions posterior between the stomach and pancreas or adhesions are released with the help of the vessel sealer. To facilitate and optimize exposure, the posterior surface of the stomach is subsequently suspended to the anterior abdominal wall with a running barbed suture [Figure 2].

Tumor location and its relation to key vascular structures are confirmed using the intraoperative ultrasound probe. The TileProTM picture overlay option enables simultaneous visualization of the ultrasound images and identification of structures in the operative field.

Next, the peritoneum overlying the inferior border of the pancreas is incised using monopolar scissors. Further dissection along the plane between the posterior aspect of the pancreas and the retroperitoneum from medial to lateral is performed. Superior mesenteric vein (SMV) and portosplenic confluence are identified as dissection and tunneling continues toward the superior border of the pancreas [Figure 3]. Robotic micro-clips are used to clip small venous branches draining directly from the pancreas into

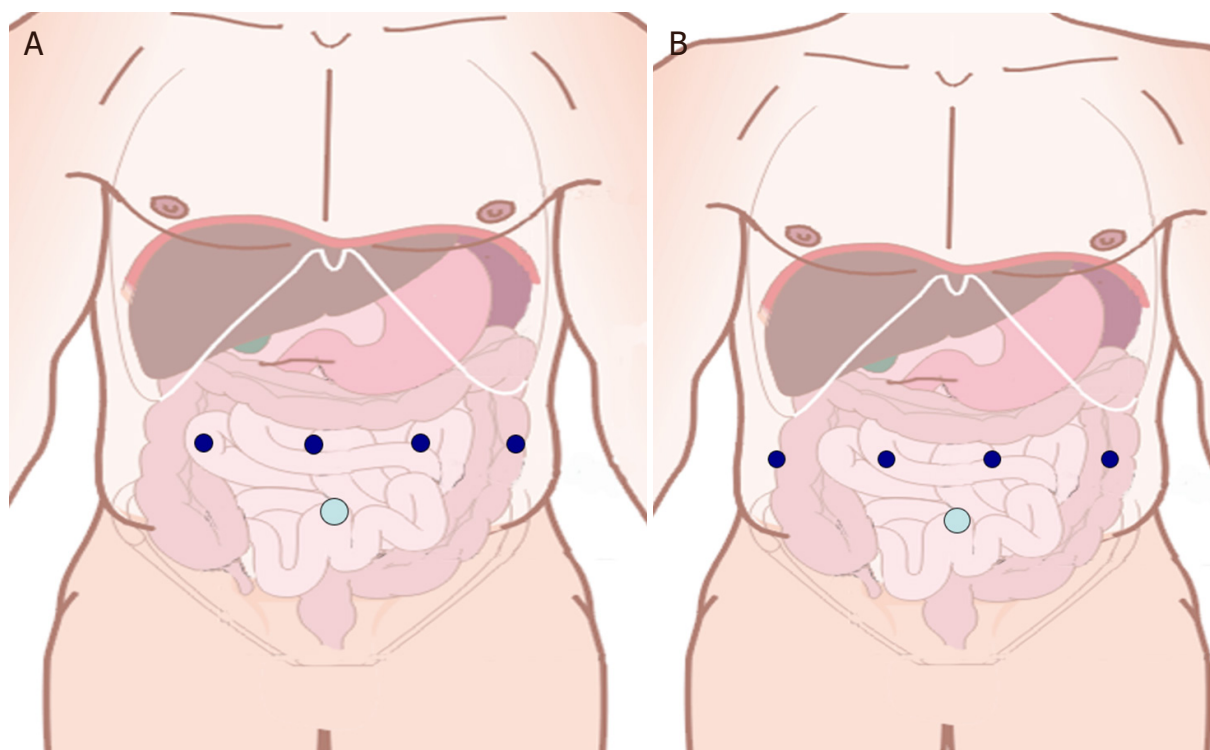


Figure 1. A: Trocar placement for robotic distal pancreatectomy; B: Trocar placement for robotic Whipple

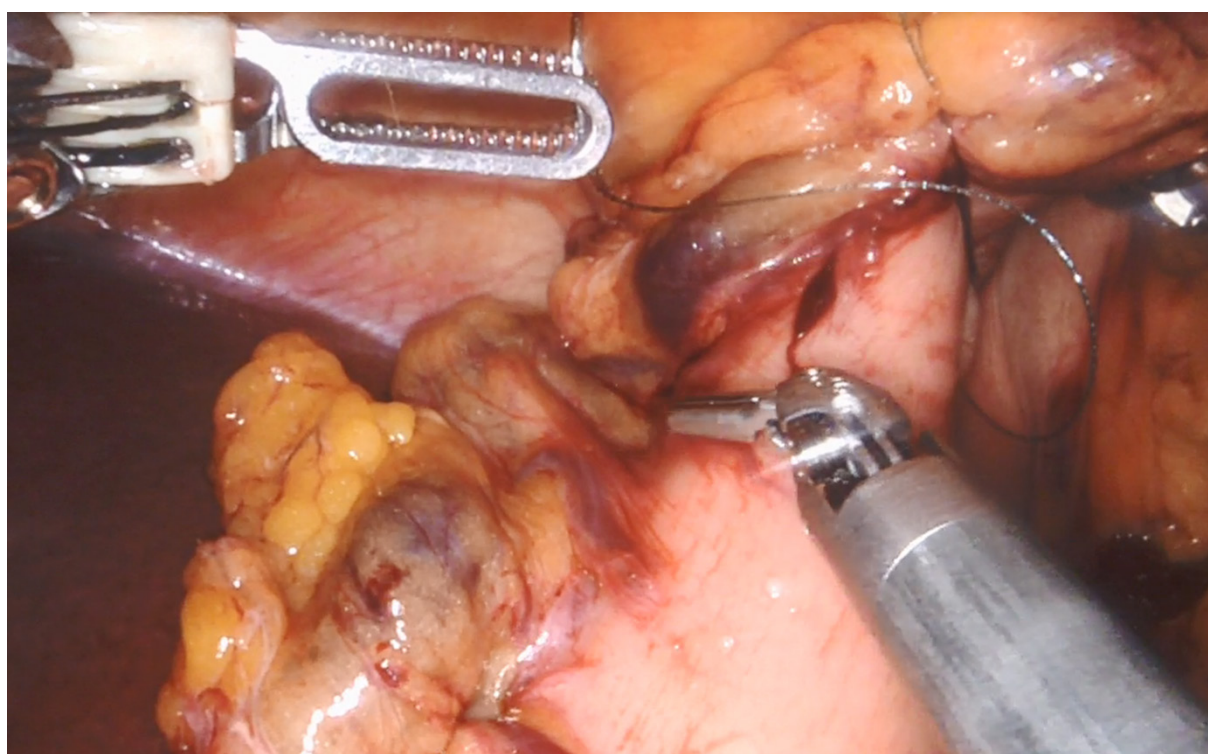


Figure 2. Suspension of the stomach

the splenic vein. The peritoneum at the superior margin of the body of the pancreas is incised. Delicate dissection to identify the splenic artery take off from the celiac trunk and concomitant lymphadenectomy is performed.

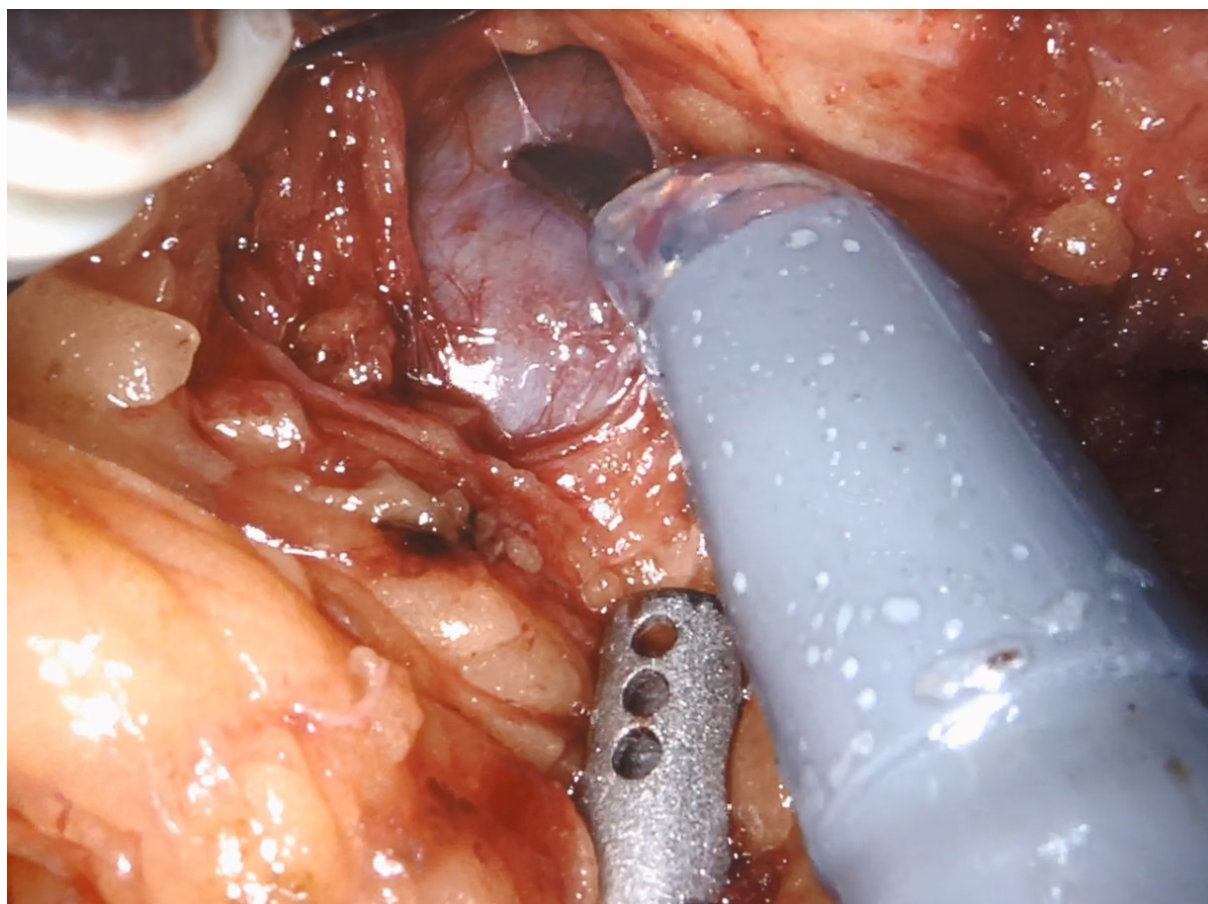


Figure 3. Tunneling between superior mesenteric vein and pancreas

Intraoperative ultrasound and also a clamping trial using bulldogs are applied to confirm doubtless identification of the splenic artery. The artery may then be divided using locking plastic clips. The neck of the pancreas is encircled via the created tunnel with a Dacron umbilical tape. Resection continues with division of the pancreas using a stapling device (robotic or laparoscopic stapler through the assistant port). The splenic vein is isolated and divided distal to the confluence applying locking plastic clips. The pancreas is then further dissected off the retroperitoneum. The specimen is placed in the retrieval bag and removed via the umbilical port, which may be enlarged to permit specimen extraction.

Robotic radical antegrade modular pancreatosplenectomy (robotic RAMPS) may be beneficial in selected patients. The mode of dissection is also from medial to lateral; however, as a more radical approach, the left renal vein is exposed and Gerota's fascia is cleared off the left kidney. The left adrenal is resected en bloc if the tumor breaks through the posterior plane. The dissection continues further posteriorly to the diaphragm using the retroperitoneal muscles as the posterior border, diaphragm as the superior border, and renal vein as the inferior border of the dissection plane. Radical lymphadenectomy including the gastrosplenic, splenic, infrapancreatic and gastroduodenal nodes is performed. In addition, lymph nodes along the celiac part of the aorta and superior mesenteric arteries are removed^[11].

ROBOTIC PANCREATODUODENECTOMY

The falciform ligament is taken down and to be used as a vascularized pedicled flap^[3]. To optimize surgical exposure of the hepatoduodenal ligament, the gallbladder is sutured to the anterior abdominal wall. In

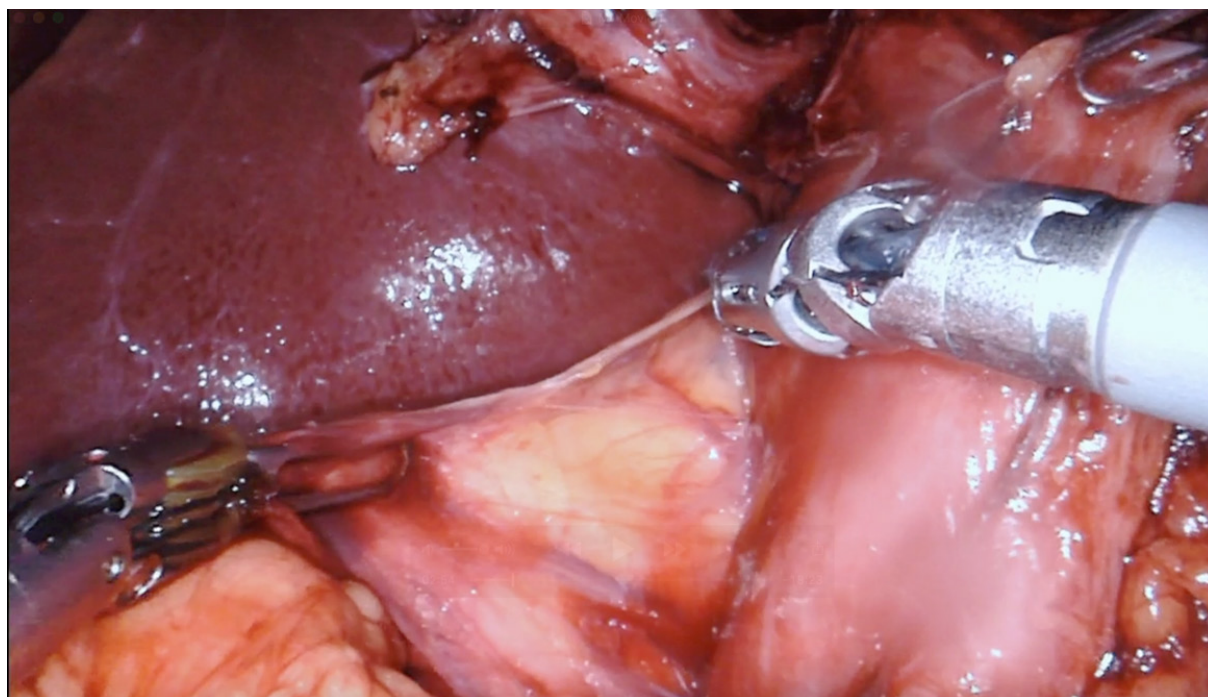


Figure 4. Kocherization

absence of a gallbladder a Nathanson retractor is introduced. The robotic vessel sealer is used to open the gastrocolic ligament and the distal gastric antrum as well as the proximal duodenum are dissected. The right gastroepiploic and right gastric artery are identified and divided between locking clips. The hepatic flexure of the colon is taken down and the duodenum Kocherized followed by the division of the proximal duodenum using a 60-mm robotic stapler [Figure 4].

TileProTM picture overlay while performing intraoperative ultrasound is used to evaluate the vasculature prior to division of vessels. Fluorescence imaging FireFlyTM assists in identifying the biliary structures. The hepatic artery is dissected, and lymphadenectomy is performed. After identification of the gastroduodenal artery and determination of its relevance for the hepatic blood supply (clamping trial), the artery is ligated using silk sutures, clipped with HemolockTM clips and divided leaving a stump on the hepatic portion [Figure 5].

The ligament of Treitz is identified. Using a robotic stapler, the jejunum is divided 20 cm distal to the ligament of Treitz. The mesentery is transected using the vessel sealer. Further dissection from the right upper quadrant enables a pull through of the proximal jejunum.

The peritoneum overlying the inferior border of the pancreas is incised, the vein of Henle (gastrocolic trunc) identified and followed towards the SMV. A tunnel between the pancreatic neck and the SMV/portal vein is created. An umbilical tape is then passed through this tunnel. Pancreatic neck transection is performed using the monopolar scissors coupled with saline irrigation. Following division of the pancreas, the uncinate process is dissected off the superior mesenteric vessels using the vessel sealer [Figure 6].

The cystic artery and duct are clipped and divided. The common hepatic duct is transected just above the take off of the cystic duct. The specimen is placed in a retrieval bag for removal at the end of surgery and meanwhile placed in the lower abdomen.

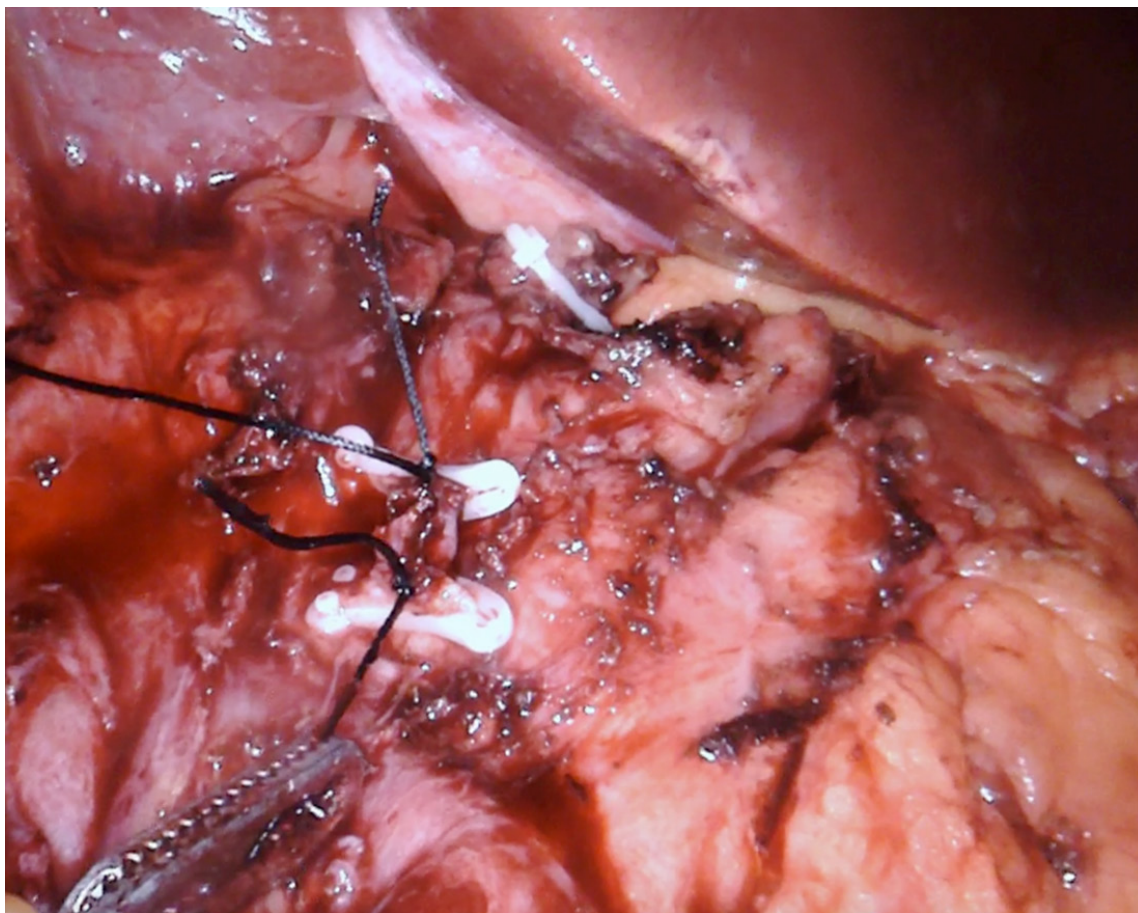


Figure 5. Transection gastroduodenal artery

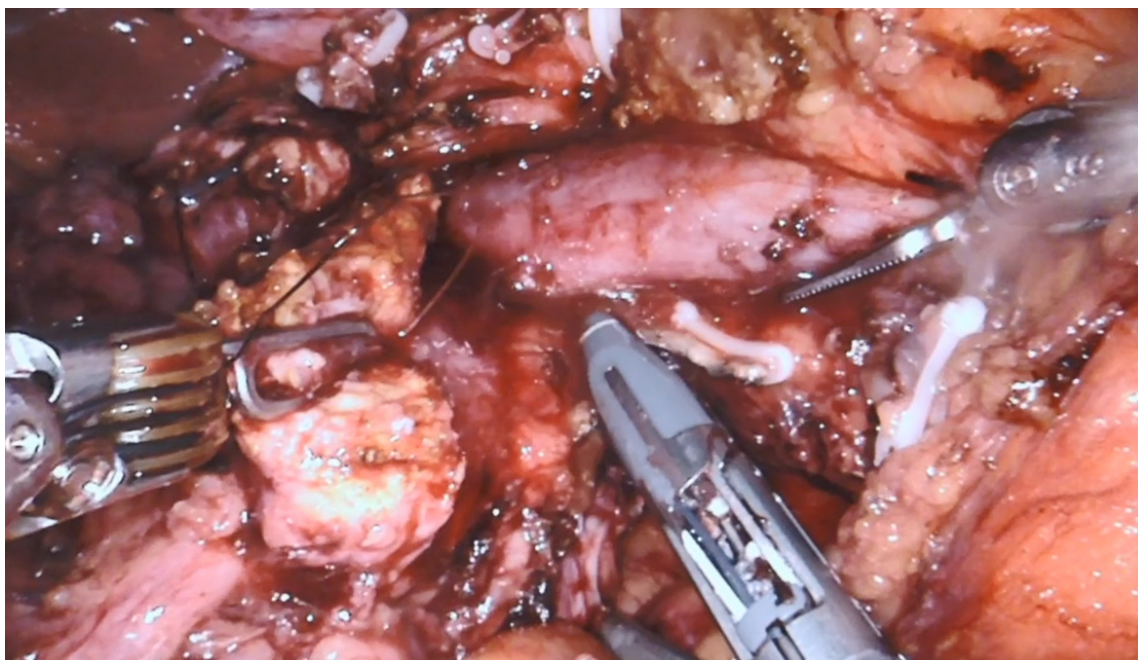


Figure 6. Transection mesopancreas

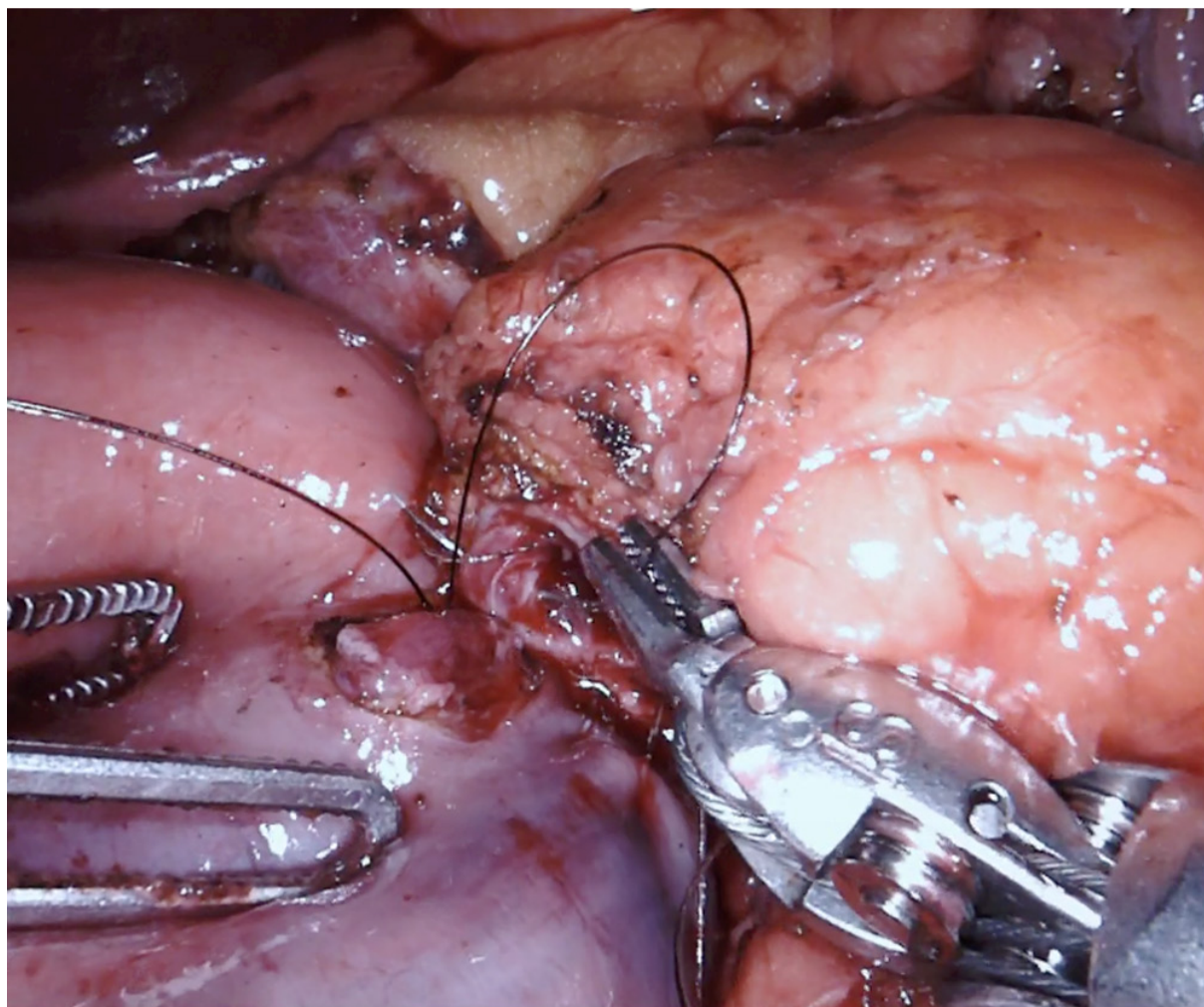


Figure 7. Pancreaticojejunostomy

A window is created in an avascular area of the transverse mesocolon, and the jejunum is pulled through. The pancreaticojejunostomy (PJ) is performed as a two-layer end-to-side anastomosis with duct to mucosa approximation. A 4-0 monofilament running suture is used to create the posterior layer of the anastomosis. Monofilament sutures (5-0) are applied to create the duct to mucosa anastomosis in interrupted fashion [Figure 7].

Stents may be used depending on the diameter of the pancreatic duct and consistency. After making a small enterotomy to the jejunum, the hepaticojejunostomy may be performed in a running (larger ducts, 4-0 barbed suture) or interrupted (smaller ducts, 4-0 or 5-0 monofilament) fashion 10-15 cm downstream from the PJ [Figure 8].

The duodenojejunostomy may be performed ante- or transmesocolic. An antimesenteric enterotomy is made, the anastomosis is performed in a seromuscular, in a single-layer running fashion using a barbed absorbable monofilament suture (4-0).

The vascularized falciform ligament flap is pulled through the empty space behind the pancreaticojejunostomy. A 19 French Blake drain is placed in proximity to the pancreatic and biliary anastomosis. Specimen extraction is performed via a Pfannenstiel incision at the surgeon's discretion^[2].

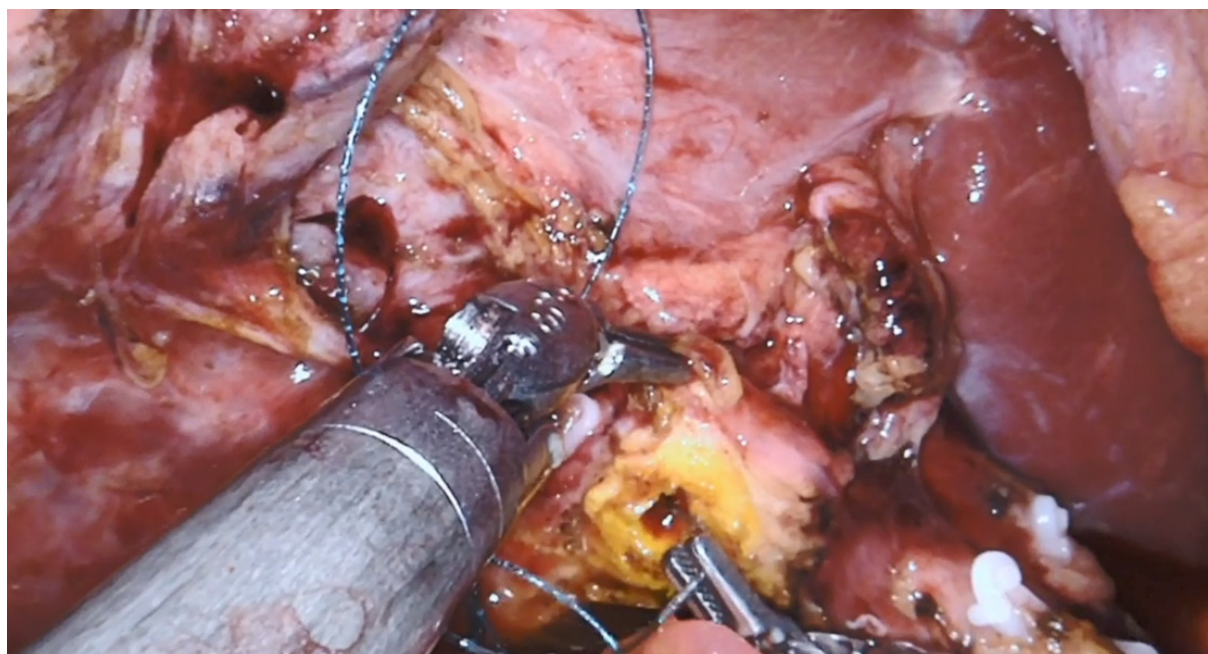


Figure 8. Hepaticojejunostomy

DISCUSSION

Robotic pancreatic surgery provides several advantages and enables the surgeon to perform complex resections and reconstructions by facilitating supraphysiological movements with the robotic instruments^[12]. Since the first report of a robotic-assisted distal pancreatectomy in 2001, total pancreatectomies, pancreatic tumor enucleations, pancreaticoduodenectomy, central pancreatectomy and Appleby procedures have been performed, indicating a promising future. Results of randomized control trials comparing robot-assisted PD with the laparoscopic or open approach are lacking. Patient recruitment for one randomized control trials in China and one in the USA started in 2020, and results are expected for 2024. The international consensus statement on robotic pancreatic surgery published last year reveals that the level of evidence still remains moderate to low for the robotic platform^[13].

A review of our own experience revealed longer operative times of approximately 136 min when compared with our open PD cohort^[14]. However, robotic PD resulted in less blood loss (200 mL lower), a shorter intensive care unit stay, a lower 30-day complication rate, and no difference in total costs compared with open PD^[15,16].

Perhaps more importantly, we found that with increasing experience, the pancreatic fistula rate could be reduced to below that of most open as well as laparoscopic series (7.4% vs. 12%) and that the robotic approach may offer improved oncologic outcomes.

The significantly higher lymph node yield and decreased inflammatory response demonstrated in robotic surgery may improve overall survival^[4,17].

Multiple single or multi-institutional retrospective studies to compare specific outcomes between robotic, laparoscopic and open approaches are reported^[6,14-16,18-24]. A large systematic review examined data from 13 retrospective series^[25]. It compared the outcomes of 738 patients who underwent robotic and open PDs between 2000 and 2016. The data showed that the robotic approach was associated with longer operative

times but lower estimated blood loss. The learning curve to decrease rates of conversion to an open procedure was found to be as high as 20 robotic PDs. Overall morbidity rates were comparable between the robot and open groups. Mortality rates also did not differ between the two approaches and ranged between 1%-12.5%. Delayed gastric emptying, however, was found to be lower with the robotic approach^[25,26]. An NSQIP study comparing 30-day outcomes between laparoscopic and robotic PDs found that there was no difference in 30-day morbidity or mortality between the two approaches^[10]. However, they did find that the rates of conversion to an open procedure were higher for patients undergoing laparoscopic PD (26% vs. 11.3%).

Increasing proficiency with robotic pancreatic surgery is reflected in a decrease in operative times as well as conversion rates. Other more sophisticated factors may include number of lymph nodes resected, blood loss, R-status, hospital stay, and 90-day complications and readmission as well^[8]. Our initial experience with robotic pancreatic surgery revealed a conversion rate of one in four decreasing to one in 32 cases after overcoming the learning curve. In line with this, procedural duration decreased significantly over time. Boone *et al.*^[12] reported that blood loss and conversion rate decrease significantly after 20 robotic PD cases. The clinically relevant Grade B/C pancreatic fistulas rate (POPF) decreased by half after 40 cases along with a significant decrease in operative times after 80 cases.

While laparoscopic skills enhance the learning curve in our experience, training in robotic surgery should be structured. In a first phase basic skills and procedure specific skills with the help of simulation, biotissue drills, video libraries, live case observations, and training courses have to be achieved^[27]. The second phase consists of fellowships, and proctoring programs to ensure patient safety during the first procedures. During the third phase the surgeon's aim is to safely implement the procedure into standard practice, while minimizing the learning curve related to excess morbidity and mortality. Adequate training and high procedural volume are key to implementing robotic pancreatic surgery safely^[28].

CONCLUSION

Robotic hepatopancreatobiliary surgery has undergone rapid evolvement over the last two decades. Its adoption has been tempered by the complexity of the procedures. The combination of superior articulation, better optics and elimination of tremor provides technical and ergonomic advantages over conventional laparoscopy. At high-volume centers, once the learning curve has been surpassed, robotic PD has been shown to be non-inferior to open PD in terms of POPF development and other perioperative outcomes. The higher operative cost of the procedure may be offset by lower hospital length of stays associated with a minimally invasive approach. However, more robust data in the form of a randomized controlled trial and other cost benefit studies are needed.

DECLARATIONS

Authors' contributions

Made substantial contributions to the design of the work, interpretation of data, and drafting and substantive revision of the manuscript: Tschuor C, Nagarkatti SS, Salibi PN, Vrochides D, Martinie JB

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John B. Martinie is a proctor for Intuitive. Christoph Tschuor's fellowship salary is granted by Intuitive.

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Review

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Percutaneous mitral balloon valvuloplasty - state of the art

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Abstract

Since its introduction in 1982, percutaneous mitral balloon valvuloplasty (PMV) has been used successfully as an alternative to open or closed surgical mitral commissurotomy in the treatment of patients with symptomatic rheumatic mitral stenosis. PMV is safe and effective and provides sustained clinical and hemodynamic improvement in patients with mitral stenosis. The immediate and long-term results appear to be similar to those of surgical mitral commissurotomy. Proper patient selection is an essential step for being able to predict the immediate results of PMV. Candidates for PMV require precise assessment of the mitral valve morphology. The Wilkin's echocardiographic score (Echo-Sc) is currently the most widely used method for predicting PMV outcome. Leaflet mobility, leaflet thickening, valvular calcification, and sub valvular disease are each scored from 1 to 4. An inverse relationship exists between the Echo-Sc and PMV success. Both immediate and intermediate follow-up studies have shown that patients with Echo-Sc ≤ 8 have superior results, significantly greater survival, and event free survival compared to patients with Echo-Sc > 8 . We identified other clinical and morphologic predictors of PMV success that include age, pre-PMV mitral valve area, history of previous surgical commissurotomy, and mitral regurgitation (MR), and post-PMV variables (e.g., post-PMV MR $\geq 3+$ and pulmonary artery pressure), that may be used in conjunction with the Echo-Sc to optimally identify candidates for PMV. This concept demonstrates a multifactorial nature of the prediction of immediate and long-term results. Other echocardiographic scores have been developed for the screening of potential candidates for PMV. They include a unique score that take into account the length of the chordae. A novel quantitative score that included the ratio of the commissural areas over the maximal excursion of the leaflets from the annulus in diastole. The components of this score include mitral valve area $\leq 1 \text{ cm}^2$, maximum leaflet displacement $\leq 12 \text{ mm}$, commissural area ratio ≥ 1.25 , and sub valvular involvement. Finally, a score that is able to identify patients who are more



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likely to develop significant mitral regurgitation post-PMV. This score takes into account the distribution (even or uneven) of leaflet thickening and calcification, the degree and symmetry of commissural disease, and the severity of subvalvular disease. The transvenous transseptal approach is the most widely used PMV technique. The two major techniques of PMV are the double-balloon technique and the Inoue technique which are equally effective techniques of PMV. Encouraging results of PMV have been reported in special mitral stenosis population cohorts including pregnant women, patients with previous surgical commissurotomy, patients with atrial fibrillation, patients with pulmonary hypertension, elderly patients, patients with calcific mitral stenosis, and patients with associated aortic regurgitation. To summarize, PMV is the preferred form of therapy for relief of mitral stenosis for a selected group of patients with symptomatic mitral stenosis and suitable valve anatomy for valvuloplasty. Patients with Echo-Sc ≤ 8 have the best results, particularly if they are young, are in normal sinus rhythm, have no pulmonary hypertension, and have no evidence of calcification of the mitral valve under fluoroscopy. The immediate and long-term results of PMV in this group of patients are similar to those reported after surgical mitral commissurotomy. Patients with Echo-Sc > 8 have only a 50% chance to obtain a successful hemodynamic result with PMV, and the long-term follow-up results are worse than those from patients with Echo-Sc ≤ 8 . In patients with Echo-Sc ≥ 12 , it is unlikely that PMV could produce good immediate or long-term results and they preferably should undergo mitral valve replacement. However, PMV could be considered in these patients if they are high-risk or unqualified surgical candidates.

Keywords: Mitral stenosis, mitral balloon valvuloplasty, rheumatic mitral stenosis

INTRODUCTION

Mitral stenosis is more often caused by rheumatic heart disease. Other causes of mitral stenosis include severe calcification of the mitral annulus and congenital defects of the mitral valve^[1-3]. Until the early 1980s, surgery was the only possible treatment for severe mitral stenosis; then, a new alternative appeared, percutaneous mitral balloon valvuloplasty (PMV). Since its introduction in 1982 by Inoue *et al.*^[4], PMV has been used successfully as an alternative to open or closed surgical mitral commissurotomy for the treatment of patients with symptomatic rheumatic mitral stenosis^[4-8]. In 1986, we performed the first percutaneous mitral balloon valvuloplasty in the United States in a 70-year-old man with end-stage mitral stenosis^[5]. What have we learned about this technique over the subsequent 34 years? In this chapter, I report an analysis of the immediate and long-term results of PMV.

PATIENT SELECTION FOR PMV

Clinical evaluation of patients with mitral stenosis is the first step of the decision to intervene. Excellent results with PMV are seen in individuals with a crisp opening snap, a Wilkin's echocardiographic score ≤ 8 , and no calcium in the commissures. The existence of an opening snap confirms the mitral valve's mobility and pliability. As the mitral valve becomes severely calcified and immobilized, the opening snap disappears and the first heart sound amplitude decreases. Appropriate patient selection is an essential step when predicting the immediate results of PMV. Candidates for PMV require precise assessment of mitral valve morphology^[7,9-12]. The assessment of the anatomy of the mitral valve is critical and it aims to eliminate contraindications and define prognostic considerations. Table 1 shows current American Heart Association/ American College of Cardiology, and European guidelines for the use of PMV^[13,14]. The presence of a left atrial thrombus is the main contraindication for the technique and requires the performance of transesophageal echocardiography before the procedure [Table 1].

As shown in Tables 2 and 3, PMV is a safe procedure that produces good immediate hemodynamic outcome, low complication rate, and clinical improvement in the majority of patients with mitral stenosis^[8,9,15-17]. The immediate and long-term results appear to be similar to those of surgical mitral

Table 1. Recommendations for percutaneous mitral valvuloplasty

Current indication	Class	Level of evidence
Asymptomatic patients with moderate or severe mitral stenosis (area < 1.5 cm ²) and valve morphology favorable for PMV who have pulmonary hypertension (PA pressure systolic > 50 mmHg at rest or 60 mmHg with exercise) in the absence of left atrium thrombus or moderate to severe MR	I	Grade A
Patients with NYHA functional class II-IV, moderate or severe mitral stenosis (area < 1.5 cm ²), a non-pliable calcific valve who are at high risk for surgery in the absence of left atrium thrombus or moderate to severe MR	Ia	Grade C
Asymptomatic patients, moderate or severe mitral stenosis (area < 1.5 cm ²) and valve morphology favorable for PMV, who has new onset of atrial fibrillation in the absence of left atrium thrombus, and moderate to severe MR	IIa	Grade B
Patients with NYHA functional Class II-IV, moderate to severe mitral stenosis (area < 1.5 cm ²), and non-pliable calcified valve who are low risk for surgery	IIb	Grade C
Patients with mild mitral stenosis	III	Grade C

Adapted from current American College of Cardiology/American Heart Association^[13] and European^[14] guidelines for the management of patients with valvular heart disease. PMV: percutaneous mitral balloon valvuloplasty; MR: mitral regurgitation; NYHA: New York Heart Association Functional Class of Heart Failure

Table 2. Immediate changes in mitral valve area after PMV

Author	Institution	# Patients	Age	Pre-PMV	Post-PMV
Palacios <i>et al.</i> ^[10]	MGH	1,085	55 ± 15	0.9 ± 0.3	1.9 ± 0.6
Lung <i>et al.</i> ^[22]	Tenon	1,024	45 ± 15	1.0 ± 0.2	1.9 ± 0.3
Hernandez <i>et al.</i> ^[17]	Clinico Madrid	561	53 ± 13	1.0 ± 0.2	1.8 ± 0.4
Stefanadis <i>et al.</i> ^[35]	Athens University	438	44 ± 11	1.0 ± 0.3	2.1 ± 0.5
Chen <i>et al.</i> ^[11]	Guangzhou	4,832	37 ± 12	1.1 ± 0.3	2.1 ± 0.2
Dean <i>et al.</i> ^[9]	Multicenter	738	54 ± 12	1.0 ± 0.4	2.0 ± 0.2
Herrmann <i>et al.</i> ^[18]	Multicenter	200	53 ± 15	1.0 ± 0.3	1.8 ± 0.7
Feldman <i>et al.</i> ^[37]	Multicenter	260	53 ± 15	1.0 ± 0.3	1.8 ± 0.6
Reyes <i>et al.</i> ^[44]	Fattouma	463	33 ± 12	1.0 ± 0.2	2.2 ± 0.4
Arora <i>et al.</i> ^[19]	G.B. Pan	600	27 ± 8	0.8 ± 0.2	2.2 ± 0.4
Cribier <i>et al.</i> ^[38,39]	Rouen	153	36 ± 15	1.0 ± 0.2	2.2 ± 0.4

Modified from Palacios IF. Percutaneous mitral balloon valvuloplasty for patients with rheumatic mitral stenosis^[1]. MGH: Massachusetts General Hospital; PMV: percutaneous mitral balloon valvuloplasty

Table 3. Complications after PMV

Author	Pts	Mortality	Tamponade	Severe MR	Embolism
Palacios <i>et al.</i> ^[10]	1,085	0.6%	0.8%	2.7%	1.2%
Vahanian <i>et al.</i> ^[16]	200	0.0%	0.3%	3.4%	0.3%
Lung <i>et al.</i> ^[22]	1,024	0.4%	0.0%	4.0%	4.0%
Hernandez <i>et al.</i> ^[17]	561	0.4%	0.6%	4.5%	
Stefanadis <i>et al.</i> ^[35]	438	0.2%	0.0%	3.4%	0.0%
Chen <i>et al.</i> ^[11]	4,832	0.1%	0.8%	1.4%	0.5%
Dean <i>et al.</i> ^[9]	738	3.0%	4.0%	3.0%	3.0%
Herrmann <i>et al.</i> ^[18]	200	0.6%	1.0%	2.4%	1.5%
Feldman <i>et al.</i> ^[37]	260	1.1%	0.7%	4.0%	0.7%
Reyes <i>et al.</i> ^[44]	463	0.4%	0.7%	4.6%	2.0%
Arora <i>et al.</i> ^[19]	600	1.0%	1.3%	1.0%	0.5%
Cribier <i>et al.</i> ^[38,39]	153	0.0%	0.7%	1.4%	0.7%

Modified from Palacios IF. Percutaneous mitral balloon valvuloplasty for patients with rheumatic mitral stenosis^[1]. PMV: percutaneous mitral balloon valvuloplasty; MR: mitral regurgitation

commissurotomy^[10,11,18-20]. Nowadays, PMV is the preferred form of therapy for relief of mitral stenosis for a selected group of patients with symptomatic rheumatic mitral stenosis.

The Wilkin's echocardiographic score (Echo-Sc) is currently the most widely used method for patient selection predicting PMV outcome^[7,12] (Figure 1, panels A and B display video loops for low and high Echo

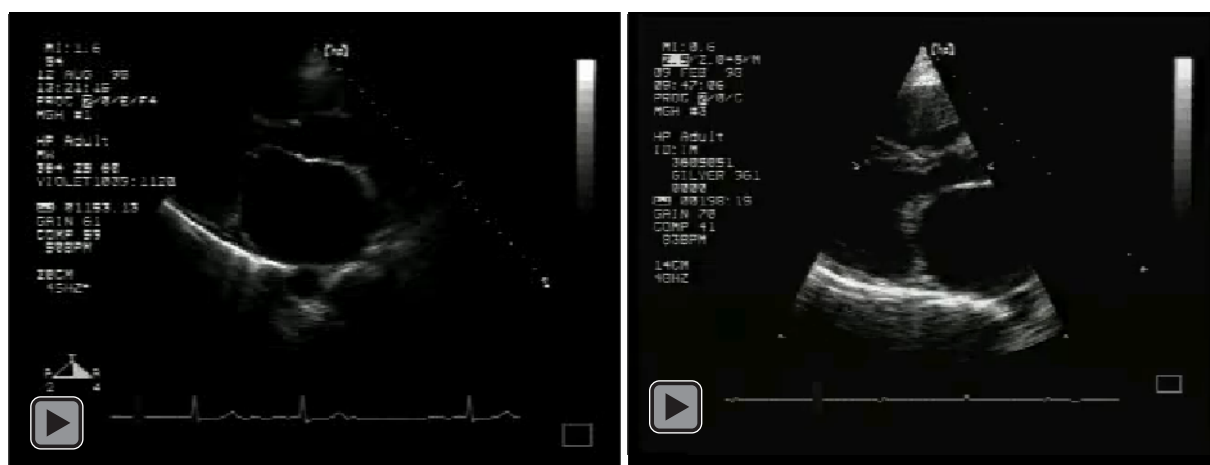


Figure 1. Video loops from a patient with severe mitral stenosis and a low Echo Score of 5 (right panel) and a high Echo Score of 10 (left panel)

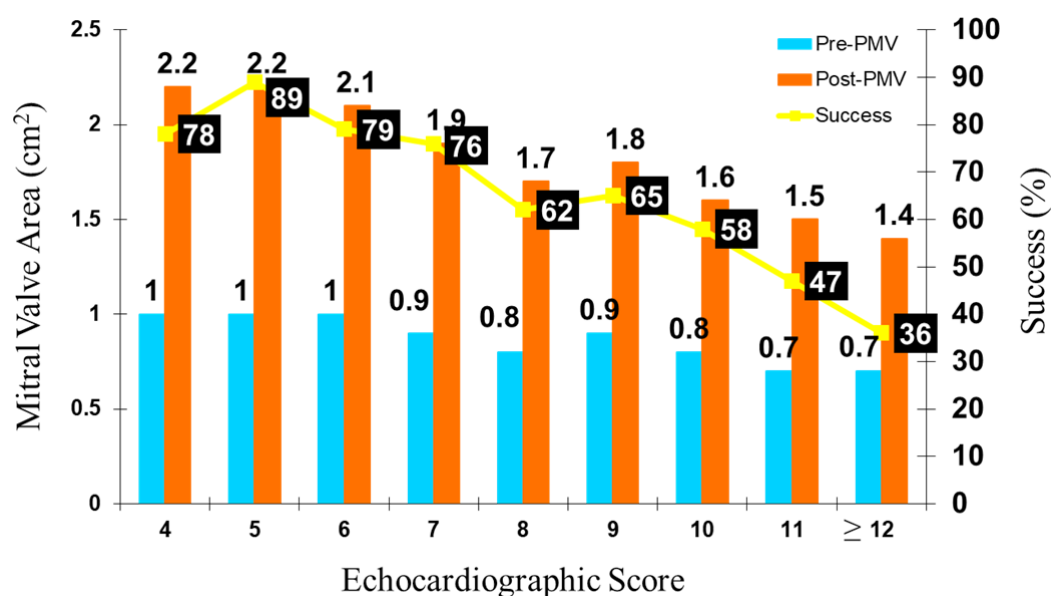
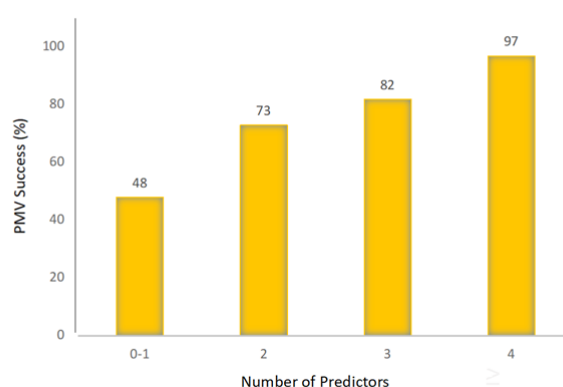


Figure 2. Relationship between the echocardiographic score and changes in mitral valve area after PMV (bar graphs), and relationship between the echocardiographic score and PMV success (line with filled yellow triangles). Numbers at the top of bar graphs represent mean mitral valve areas before (blue bars) and after (orange bars) PMV for each echocardiographic score. Percentages in black squares represent PMV success rate at each echocardiographic score. Modified from Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC^[1,13,18]. PMV: percutaneous mitral balloon valvuloplasty

scores, respectively). Leaflet mobility, leaflet thickening, valvular calcification, and sub valvular disease are each scored from 1 to 4, yielding a maximum total Echo-Sc of 16^[9,12]. As shown in Figure 2, an inverse relationship exists between Echo-Sc and PMV success. Both immediate, and intermediate follow-up studies have shown that patients with Echo-Sc ≤ 8 have superior results and significantly greater survival and combined event free survival than patients with Echo-Sc > 8^[7,12-14]. Long-term follow-up results of PMV are limited^[9,10,15-17]. Although earlier studies have reported that PMV results in good immediate hemodynamic and clinical improvement in most patients with rheumatic mitral stenosis, superior long-term follow-up results are seen in a selected group of patients with Echo- Sc ≤ 8^[7,8,10,12,15]. We have reported that in addition to the Wilkin's Echo-Sc there are other clinical and morphologic predictors of immediate and long-term PMV success.

Multifactorial Determinants of PMV Procedural Success



Sanchez M, Cruz, I, Palacios IF, et al. 2006.

Figure 3. Multifactorial determinants of immediate and long-term outcomes from PMV. Six independent predictors of PMV success were identified: age less than 55 years, New York Heart Association classes I and II, pre-PMV mitral area of 1 cm² or greater, pre-PMV mitral regurgitation grade ≤ 2 +, echocardiographic score of ≤ 8 and male sex. Modified from Cruz-Gonzalez I, Sanchez-Ledesma M, Sanchez PL, Martin-Moreiras J, Jneid H, Rengifo-Moreno P, Inglessis-Azuaje I, Maree AO, Palacios IF^[21]. PMV: percutaneous mitral balloon valvuloplasty

Cruz-Gonzalez *et al.*^[21] developed a multifactorial score derived from clinical, anatomic, echocardiographic, and hemodynamic variables to predict procedural success and clinical outcome. Six independent predictors of PMV success were identified: age less than 55 years, New York Heart Association classes I and II, pre-PMV mitral valve area of less than 1 cm², pre-PMV mitral regurgitation Seller's grade ≤ 2 +, echocardiographic score of ≤ 8, and male sex. A score was constructed from the arithmetic sum of variables present per patient [Figure 3]. Procedural success rates increased incrementally with increasing score (0% for 0/6, 39.7% for 1/6, 54.4% for 2/6, 77.3% for 3/6, 85.7% for 4/6, 95% for 5/6, and 100% for 6/6; $P < 0.001$). In a validation cohort ($n = 285$ procedures), the multifactorial score remained a significant predictor of PMV success ($P < 0.001$). Comparison between the new score and the Wilkin's Echo-Sc confirmed that the new index was more sensitive and specific ($P < 0.001$). This new score also predicts long-term outcomes ($P < 0.001$). They concluded that clinical, anatomic, and hemodynamic variables predict PMV success and clinical outcome and may be formulated in a scoring system that would help to identify the best candidates for PMV^[21] [Figure 3].

A simpler echocardiographic score for the stenotic mitral valve was introduced by Vahanian *et al.*^[16] and Lung *et al.*^[22]. The Cormier score is unique for taking the length of the chordae into consideration. More recently, a novel quantitative score was described by Nunes *et al.*^[23], it included the ratio of the commissural areas over the maximal excursion of the leaflets from the annulus in diastole. Independent predictors of outcome were assigned a point value proportional to their regression coefficients: mitral valve area ≤ 1 cm², maximum leaflet displacement ≤ 12 mm, commissural area ratio ≥ 1.25, and sub valvular involvement^[24]. Three risk groups were defined: low (score of 0-3), intermediate (score of 5), and high (score of 6-11), with observed suboptimal PMV results of 16.9%, 56.3%, and 73.8%, respectively. The use of the same scoring system in the validation cohort yielded suboptimal PMV results of 11.8%, 72.7%, and 87.5% in the low-, intermediate-, and high-risk groups, respectively ($P < 0.0001$). Long-term outcome was predicted. The model improved risk classification in comparison with the Wilkins score (net reclassification improvement, 45.2%; $P < 0.0001$). Long-term outcome was predicted by age and postprocedural variables, including mitral regurgitation, mean gradient, and pulmonary pressure^[23].

Severe mitral regurgitation after PMV is a major complication of this procedure. This complication confers an adverse prognosis and frequently requires intensive treatment and urgent mitral valve surgery. Although some morphologic features of the mitral valve might increase the risk of severe regurgitation, echocardiographic evaluation with the Wilkin's Echo-Sc has been unable to predict it. Padial *et al.*^[25,26] described a new echocardiographic score that can predict the development of severe mitral regurgitation after PMV with the double balloon and the Inoue balloon techniques. This score takes into account the distribution (even or uneven) of leaflet thickening and calcification, the degree and symmetry of commissural disease, and the severity of sub valvular disease. Thus, echocardiography can identify patients with a high risk of developing severe mitral regurgitation after PMV using this proposed mitral regurgitation echocardiographic score^[25-27]. This new score can help assess the probability of this complication before the procedure to anticipate the likelihood that surgical repair may be needed. In addition, it could conceivably be used to select patients for modified procedure techniques that might be developed to minimize this complication^[25,26]. Anwar *et al.*^[28] used a new real-time three-dimensional echocardiography (RT3DE) score for evaluating patients with mitral stenosis (MS) and compared with Echo-Sc. The new RT3DE score was constructed by dividing each mitral valve (MV) leaflet into 3 scallops and was composed of a total of 31 points (indicating increasing abnormality), including 6 points for thickness, 6 for mobility, 10 for calcification, and 9 for subvalvular apparatus involvement. The total RT3DE score was calculated and defined as mild (< 8), moderate (8-13), or severe (≥ 14). Mitral valve morphology was assessed using the Wilkin's Echo-Sc and compared with the new RT3DE score. They reported that the new RT3DE score is feasible and highly reproducible for the assessment of mitral valve morphology in patients with mitral stenosis and it can provide incremental prognostic information in addition to the Wilkin's Echo-Sc^[28]. However, none of the scores available have been shown to be superior to the others.

COMMISSURAL CALCIFICATIONS AND DEGREE OF COMMISSURAL FUSION AND FEASIBILITY AND EFFICACY OF PMV

Although echocardiographic scores are important for identifying optimal candidates for PMV, there are other distinctive morphologic features of mitral valve disease whose relationships to outcome after percutaneous mitral valvotomy are also important. Several scores have been developed that take into account the uneven distribution of anatomic abnormalities, in particular in commissural areas^[7,25-27,29]. Since commissural splitting is the dominant mechanism by which mitral valve stenosis is relieved by this technique, commissural morphology may predict outcome. Figure 4 depicts short axis TTE of one patient with concentric mitral stenosis (right panel) and one patient with eccentric calcification mitral stenosis (left panel). For example, excessive thickening and calcification of one commissure should be expected to decrease the effectiveness of the procedure by limiting the splitting of the involved side of the orifice and predisposing the contralateral commissure to rupture or the normal leaflet to tearing. This could also potentially predispose to severe mitral regurgitation after PMV^[25-27,30]. Patients with evidence of calcium in a commissure have a lower survival rate and a higher incidence of mitral valve replacement and all end points combined. Thus, the simple presence or absence of commissural calcification assessed by two-dimensional echocardiography can be used to predict outcome^[25-27,31,32].

TECHNIQUE OF PMV

The transvenous transseptal approach is the most widely used PMV technique. Transseptal catheterization is the first step of the procedure and one of the most crucial one. The trans-arterial approach could represent an alternative in the rare cases in which the transseptal approach is contraindicated or impossible^[33-35]. There are currently two main transseptal PMV techniques, balloon valvuloplasty and metallic commissurotomy. The two major techniques of balloon valvuloplasty are the double-balloon technique and the Inoue technique. The double-balloon technique [Figure 5] is effective but demanding and carries the risk of left ventricular perforation by the guidewires or the tip of the balloons^[1,5,6,8,10]. The

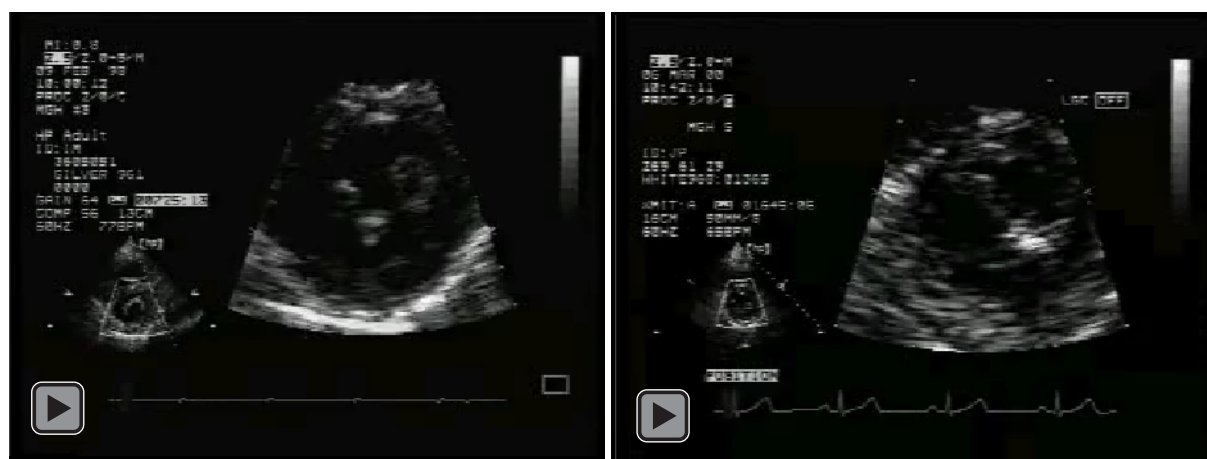


Figure 4. Short axis video loops from a patient with severe mitral stenosis and Concentric MS (right panel) and one patient with Eccentric MS (left panel). MS: mitral stenosis

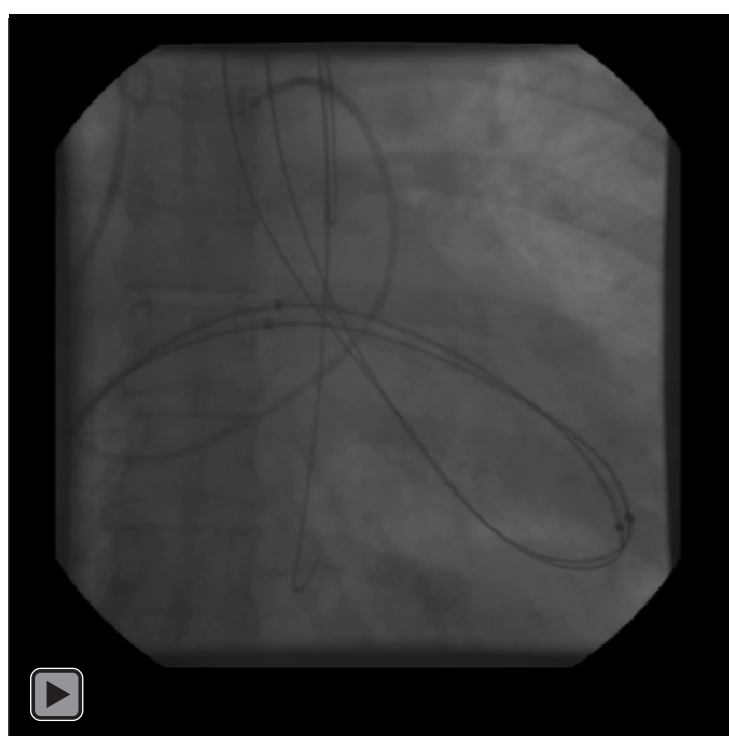


Figure 5. Double balloon mitral valvuloplasty

multi-track system [Figure 6] is a variant of the double-balloon technique and aims to make the procedure easier through the use of a monorail balloon and only a single guidewire^[36]. The Inoue technique [Figure 7] has become the most popular technique worldwide^[4,16,18,22,37]. The design of the Inoue balloon allows safe and fast positioning across the valve. In addition, it is pressure extensible, allowing for the performance of a stepwise dilatation [Figure 7]. The available data comparing the Inoue technique and the double-balloon technique suggest that the Inoue technique makes the procedure easier, and that both techniques have equivalent efficacy. Although the double-balloon technique may result in a slightly larger post-PMV valve area, the long-term results are equivalent. Furthermore, the Inoue balloon carries a lower risk because the risk of left ventricular perforation is virtually avoided^[16,23,37].

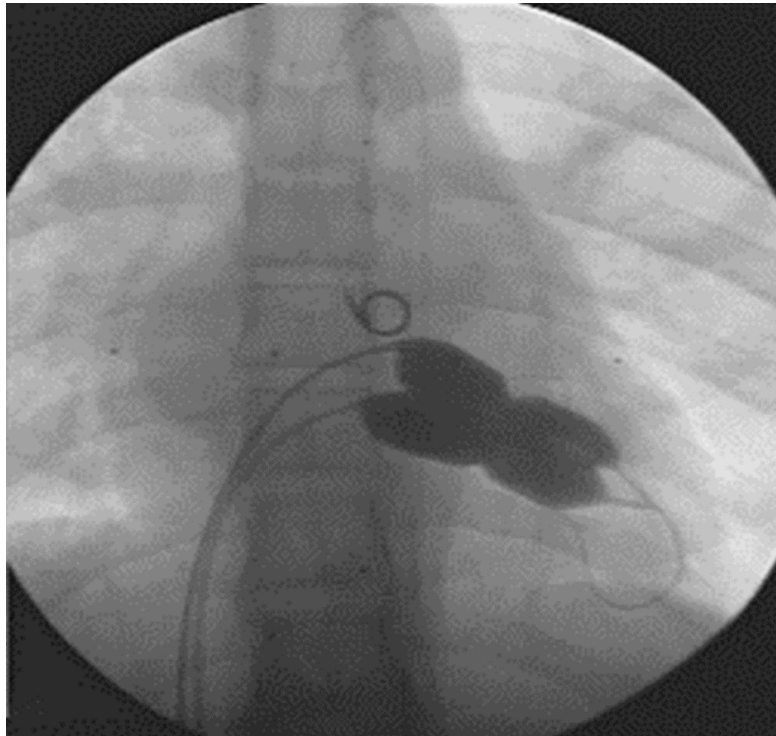


Figure 6. Double balloon percutaneous mitral balloon valvuloplasty using the multitrack balloon catheter

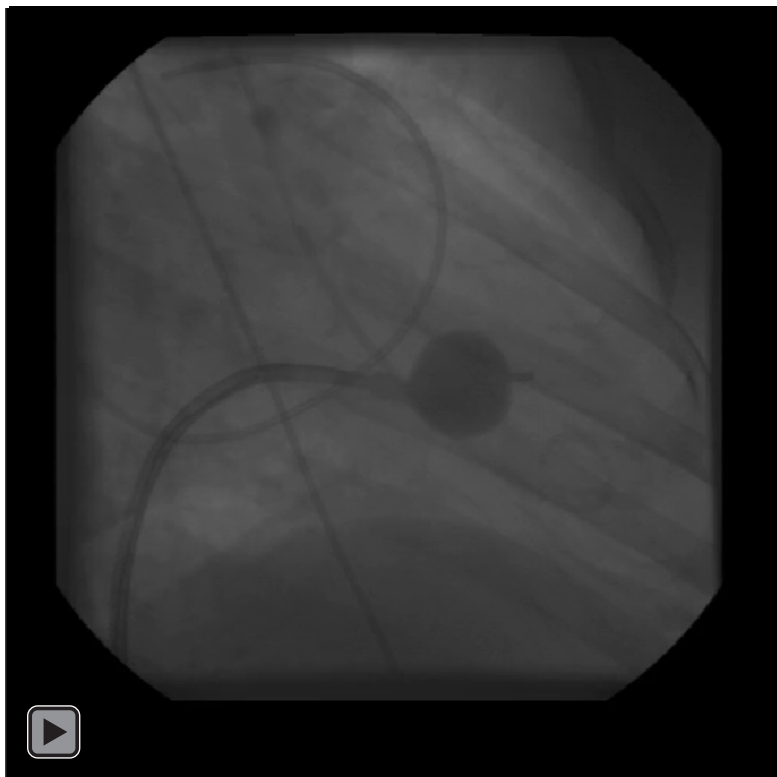


Figure 7. The Inoue balloon technique of percutaneous mitral balloon valvuloplasty

PMV is performed as previously described^[1,2,5,6]. All patients should undergo diagnostic right and left, and transseptal left heart catheterization^[1,2,5,6]. Following transseptal left heart catheterization, systemic anticoagulation is achieved by the intravenous administration of 100 units/kg of heparin. In patients older than 40 years, coronary angiography should also be performed. Hemodynamic measurements, cardiac output, and cine left ventriculography are performed before and after PMV. Cardiac output is measured by thermodilution and Fick method techniques. An oxygen diagnostic run is performed after PMV to determine the presence of significant left to right shunt across the interatrial septum after PMV.

THE ANTEGRADE DOUBLE-BALLOON TECHNIQUE

PMV using the antegrade double-balloon technique [Figure 5] is performed as previously described^[1,2,5,6]. A 7F flow directed balloon catheter is advanced through the transseptal sheath across the mitral valve into the left ventricle^[1,2,5,6]. The catheter is then advanced through the aortic valve into the ascending and then the descending aorta. A 0.889 mm or 0.9652 mm, 260 cm long Teflon coated exchange wire is then passed through the catheter. The sheath and the catheter are removed leaving the wire behind. A 5 mm balloon dilating catheter occasionally is used to dilate the atrial septum. A second exchange guide wire is passed parallel to the first guide wire through the same femoral vein and atrial septum punctures using a double lumen catheter. The double lumen catheter is then removed leaving the two guide wires across the mitral valve in the ascending and descending aorta. During these maneuvers care should be taken to maintain large and smooth loops of the guide wires in the left ventricular cavity to allow appropriate placement of the dilating balloons. If a second guide wire cannot be placed into the ascending and descending aorta, a 0.9652 mm Amplatz type transfer guide wire with a preformed curlew at its tip can be placed at the left ventricular apex. In patients with aortic valve prosthesis, two Amplatz type transfer guide wires with preformed curlew tips should be placed at the left ventricular apex. When one or both guide wires are placed in the left ventricular apex, the balloons should be inflated sequentially. Care should be taken to avoid forward movement of the balloons and guide wires to prevent left ventricular perforation. Two balloon dilating catheters, chosen according with the patient's body surface area, are then advanced over each one of the guide wires and positioned across the mitral valve parallel to the longitudinal axis of the left ventricle. The balloon valvuloplasty catheters are then inflated by hand until the indentation produced by the stenotic mitral valve is no longer seen. Generally, one, but occasionally two or three, inflations are performed. After complete deflation, the balloons are removed sequentially. The Multi-track system [Figure 6] introduced by Bonhoeffer, shares the advantages of the traditional double-balloon technique^[36]. It is safer and reduces the risk of accidental balloon displacement. The procedure is easier to perform as it only requires the presence of a single guide wire and therefore procedure times are reduced. The system is versatile and can be used in other indications. With this technique, two separate balloon catheters are positioned on a single guidewire. The first catheter, with only a distal guidewire lumen, is introduced into the vein and then advanced into the mitral orifice. Subsequently, a rapid exchange balloon catheter running on the same guidewire is inserted and lined up with the first catheter so the two are positioned side by side. Both balloons are then inflated simultaneously^[36].

THE INOUE TECHNIQUE OF PMV

Nowadays, PMV is more frequently performed using the Inoue technique as previously reported [Figure 7]^[4,16,18,22,37]. The Inoue balloon is a 12 French shaft, coaxial, double lumen catheter, made of a double layer of rubber tubing with a layer of synthetic micromesh in between. After transseptal catheterization, a stainless-steel guide wire is advanced through the transseptal catheter and placed with its tip coiled into the left atrium and the transseptal catheter removed. Subsequently, a 14 French dilator is advanced over the guide wire and used to dilate the femoral vein and the atrial septum. An Inoue balloon catheter chosen according to the patient's height is advanced over the guide wire into the left atrium. The distal part of the balloon is inflated and advanced into the left ventricle with the help of the spring wire stylet

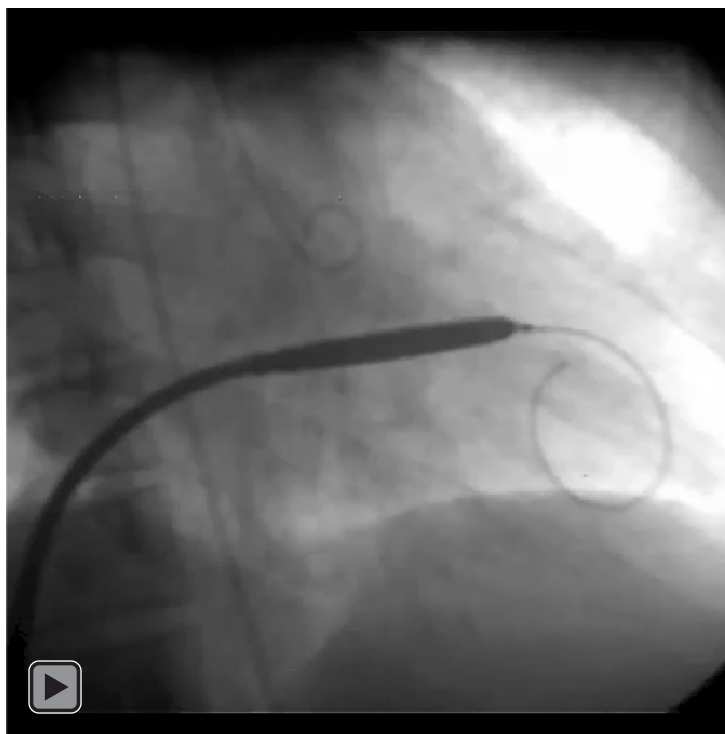


Figure 8. The Cribier metallic dilator technique of percutaneous mitral balloon valvuloplasty

which has been inserted through the inner lumen of the catheter. Once the catheter is in the left ventricle, the partially inflated balloon is moved back and forth inside the left ventricle to assure that it is free of the chordae tendineae. The catheter is then gently pulled against the mitral plane until resistance is felt. The balloon is then rapidly inflated to its full capacity and then deflated quickly. During inflation of the balloon an indentation should be seen in its middle portion. The catheter is withdrawn into the left atrium and the mitral gradient and cardiac output are measured. If further dilations are required, the stylet is introduced again, and the sequence of steps described above are repeated at a larger balloon volume. After each dilatation, its effect should be assessed by pressure measurement, auscultation, and 2D-echocardiography. If mitral regurgitation occurs or worsens, further dilation of the valve should not be performed.

A RETROGRADE TECHNIQUE OF PMV

In the retrograde technique of PMV described by Babic^[33], the balloon dilating catheters are advanced percutaneously through the right and left femoral arteries over guide wires that have been snared from the descending aorta^[33]. With the Babic technique these guide wires have been advanced transeptally from the right femoral vein into the left atrium, the left ventricle, and then the ascending aorta^[33]. A transaortic retrograde non-transseptal technique of PMV has been described by Stefanadis^[34,35].

A METALLIC VALVULOTOMY CATHETER TECHNIQUE OF PMV

A technique of PMV using a newly designed metallic valvulotomy catheter was introduced by Cribier *et al.*^[38,39] [Figure 8]. The device consists of a detachable metallic cylinder with 2 articulated bars screwed onto the distal end of a disposable catheter whose proximal end is connected to activating pliers. Squeezing the pliers opens the bars up to a maximum of 40 mm. The results with this device are at least comparable to those of the other balloon techniques of PMV. However, multiple uses after sterilization should markedly decrease procedural costs^[38,39].

Transseptal Left Heart Catheterization

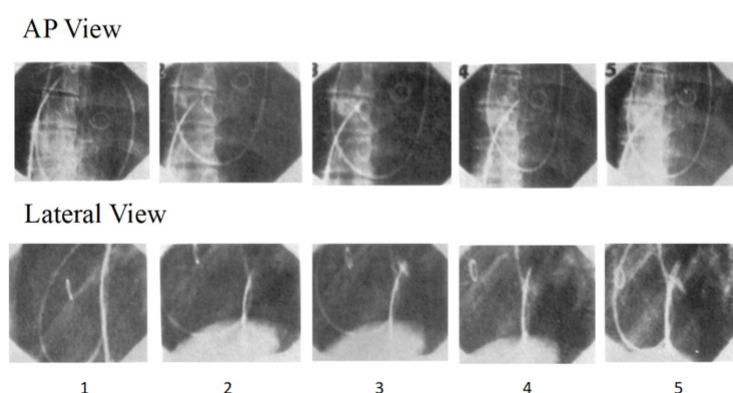


Figure 9. Transseptal left heart catheterization as viewed by anteroposterior (upper) and lateral fluoroscopy (bottom). Modified from Roelke M, Smith AJ, Palacios IF. The technique and safety of transseptal left heart catheterization: the Massachusetts General Hospital experience with 1,279 procedures^[51]

TRANSSEPTAL LEFT HEART CATHETERIZATION

Transseptal catheterization is performed using the percutaneous technique from the right femoral vein as previously described^[40,41]. Biplane fluoroscopy, if available, is the ideal imaging system. However, a single plane “C” arm fluoroscope, which can be rotated from the antero-posterior to lateral position, may also be used [Figure 9]. A pigtail catheter is positioned retrogradely in the right coronary sinus to correctly identify the aorta [Figure 9]. A detailed description of the procedure is well outlined in the article by Roelke *et al.*^[40]. The use of transesophageal or intracardiac echocardiography add on the safety and success of the procedure^[40,41]. When positioned at the target septal spot, the tip of the Brockenbrough needle is advanced into the left atrium under continuous fluoroscopic, echocardiographic and pressure monitoring. Septal penetration is heralded by a change from the right atrial to left atrial pressure measurement and by injecting contrast, which should flow freely into the left atrium. Slight variations in the technique may be required with different interventional procedures [Figure 10]. During double balloon PMV and with the Cribier metallic valvulotomy catheter, a low puncture site in the middle posterior third of the septum provides a straight pathway to the mitral orifice and apex of the left ventricle to facilitate manipulation of guidewires and catheters. A slightly higher puncture is preferred when using a single Inoue balloon to allow the straightest course for the flow directed distal balloon through the mitral valve [Figure 10].

IMMEDIATE RESULTS

The technique of PMV has now been evaluated in several thousands of patients with different clinical situations. Immediate and long-term results of PMV can be assessed in the catheterization laboratory using hemodynamics or by echocardiography^[42,43]. The use of echocardiography in the catheterization laboratory during PMV is important because it enables the detection of early complications and provides essential information on the course of the mitral valve opening. The following criteria been proposed for the desired end point of the procedure: post-PMV mitral valve area (MVA) $\geq 1.5 \text{ cm}^2$ or $>1.0 \text{ cm}^2/\text{m}^2$ body surface area or $\geq 50\%$ increase in post-PMV MVA, complete opening of at least 1 commissure, and appearance or increment of mitral regurgitation $> 1+$ in the Sellers 0 to 4+ classification^[39]. After the procedure, the most accurate evaluation of valve area is given by echocardiography using planimetry whenever possible; 3D-echocardiography may be helpful to assess the post-dilation results in terms of anatomical effects and changes of residual mitral regurgitation. PMV usually allows for a doubling in valve area, with a final valve

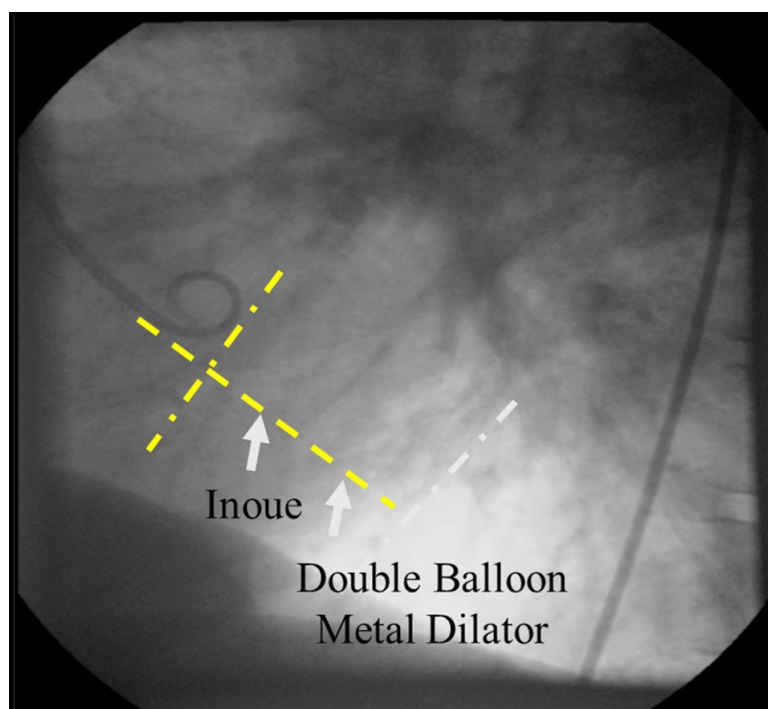


Figure 10. More selective site of transseptal puncture according procedure to be performed after completion of successful transseptal left heart catheterization. Modified from Palacios IF. Percutaneous mitral balloon valvuloplasty for patients with rheumatic mitral stenosis. In: Herrmann HC, editor^[1], with permission

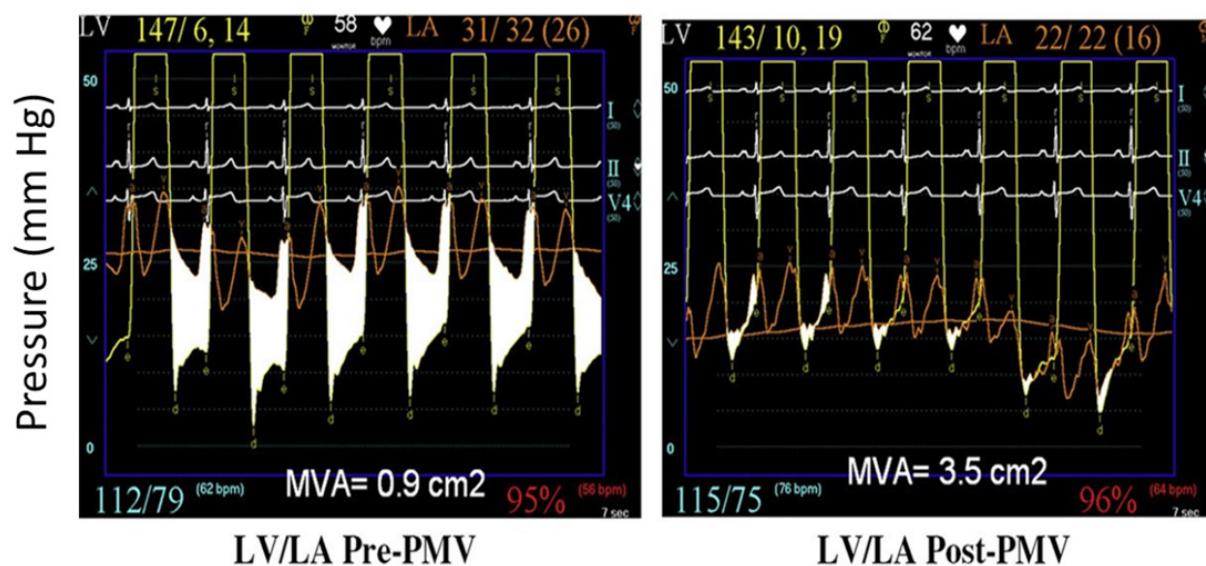


Figure 11. Hemodynamic changes produced by a successful PMV in one patient with severe mitral stenosis. Simultaneous left atrium (LA) and left ventricular (LV) pressures before (left) and after (right) double balloon PMV. The corresponding calculated MVAs are also displayed (From Palacios IF. Percutaneous mitral balloon valvuloplasty for patients with rheumatic mitral stenosis. In: Herrmann HC, editor. *Interventional Cardiology: Percutaneous Noncoronary Intervention*^[1], with permission). PMV: percutaneous mitral balloon valvuloplasty; MVA: mitral valve area

area $> 2.0 \text{ cm}^2$ on average. The improvement in valve function results in an immediate decrease in left atrial and pulmonary pressures both at rest and during exercise. [Figure 11](#) depicts the pre-PMV and post-PMV hemodynamic of one patient who underwent a successful and optimal PMV using the double-balloon

technique. PMV resulted in a substantial decrease in trans mitral gradient and an increase in MVA from 0.9 cm^2 to 3.5 cm^2 . Table 2 depicts changes in mitral valve area after PMV from different institutions with large PMV series.

The predictors of the immediate results of PMV are multifactorial. In addition to the morphological factors, preoperative variables (such as age, history of previous surgical commissurotomy, New York Heart Association functional class of heart failure, smaller initial mitral valve area, and presence of tricuspid regurgitation), and procedural factors (such as the non-use of Inoue technique) have been identified as independent predictors of poor immediate results of PMV^[6,10,15,16].

MECHANISM OF PMV

The mechanism of successful PMV is splitting of the fused commissures toward the mitral annulus, resulting in commissural widening. This mechanism has been demonstrated by pathologic, surgical, and echocardiographic studies^[7,12,42,43]. In addition, in patients with calcific mitral stenosis, the balloons could increase mitral valve flexibility by the fracture of the calcified deposits in the mitral valve leaflets. Although rare, undesirable complications, such as leaflets tears, left ventricular perforation, tear of the atrial septum, and rupture of chordae, mitral annulus, and papillary muscle, could also occur^[44].

RISKS AND COMPLICATIONS

The failure rates range from 1% to 15%, and they reflect primarily the learning curve of the operators^[8,9,12,16,37]. Table 3 depicts rate of complications from PMV from different centers with high volume of PMV. Procedural mortality ranges from 0% to 3%. The incidence of hemopericardium varies from 0.5 to 12%. Embolism is encountered in 0.5% to 5% of cases. Severe mitral regurgitation is the most worrying complication^[21,25,26,37]. It occurs in 2% to 10% of patients and results from non-commissural leaflet tearing, primarily in cases with unfavorable anatomy, and even more so if there is a heterogeneous distribution of the morphological abnormalities^[25,26]. Surgery is often necessary later and can be conservative in cases with less severe valve deformity. Although urgent surgery is seldom needed for complications (< 1% in experienced centers), it may be required for massive hemopericardium or, less frequently, for severe mitral regurgitation, leading to hemodynamic collapse or refractory pulmonary edema. Immediately after PMV, color Doppler echo shows small interatrial shunts in most patients. PMV is associated with a 15% incidence of left-to-right shunt immediately after the procedure. The pulmonary-to-systemic flow ratio is < 1.5:1 in the majority of the patients. The incidence of left-to-right shunt through the atrial communication is greater in patients with echocardiographic scores > 8^[45]. Casale *et al.*^[45] reported the results of post-PMV left to right shunting in 150 patients who underwent PMV at the Massachusetts General Hospital. A left to right shunt through the created atrial communication was present in 28 patients (19%) after PMV^[46]. The pulmonary to systemic flow ratio was > 2:1 in 4 patients and < 2:1 in 24. Univariate predictors of left to right shunting after valvuloplasty included older age ($P < 0.01$), lower cardiac output before mitral valvuloplasty ($P < 0.01$), higher New York Heart Association functional class before PMV ($P < 0.05$), presence of mitral valve calcification under fluoroscopy ($P < 0.01$) and higher Echo-Score ($P < 0.05$). Multiple stepwise logistic regression analysis identified the presence of mitral valve calcification ($P < 0.02$) and lower cardiac output ($P < 0.02$) as independent predictors of a left to right shunt through the atrial communication after PMV. A persistent atrial septal defect was demonstrated by oximetry in only 5 of 13 patients who underwent elective right heart catheterization at 11 ± 1 months after mitral valvuloplasty. Doppler color flow echo cardiography demonstrated a left to right shunt in only one of the remaining three patients who did not undergo catheterization. Thus, 13 (59%) of 22 patients who had a left to right shunt after PMV were demonstrated to have no evidence of residual left to right shunt through the created atrial communication at 10 ± 1 -month follow-up study^[45].

Table 4. Clinical long-term follow-up after PMV

Author	# Patients	Age	Follow up (years)	Survival	Event-free
Palacios <i>et al.</i> ^[10]	879	55	12	87%	53%
Lung <i>et al.</i> ^[22]	1,024	49	10	85%	56%
Hernandez <i>et al.</i> ^[17]	561	53	7	95%	69%
Orrange <i>et al.</i> ^[64]	132	44	7	83%	65%
Reyes <i>et al.</i> ^[65]	30	29	7	100%	90%
Stefanadis <i>et al.</i> ^[35]	441	44	9	98%	75%

Modified from Palacios IF. Percutaneous mitral balloon valvuloplasty for patients with rheumatic mitral stenosis^[1]. PMV: percutaneous mitral balloon valvuloplasty

LONG-TERM RESULTS

We are now able to analyze follow-up data up to 15 years^[9,12-14,16]. Several large single-center series confirm the late efficacy of PMV in a large population comprising a variety of patient subsets [Table 4]. Late outcome after PMV differs according to the quality of the immediate results. In a series of 879 patients undergoing PMV at the Massachusetts General Hospital, we reported a completed follow-up in 575 (96%) of patients with Echo-Sc ≤ 8 and in 269 (97%) of patients with Echo-Sc > 8 ^[9]. For the entire population, there were 110 (12.5%) deaths (25 of which were non-cardiac), 234 (26.6%) mitral valve replacements (MVRs), and 54 (6.14%) redo PMVs, accounting for a total of 398 (45.3%) patients with combined events (death, MVR, or redo PMV). Of the remaining 446 patients that were free of combined events, 418 (94%) were in New York Heart Association (NYHA) class I or II. Follow-up events occurred less frequently in patients with Echo-Sc ≤ 8 and included 51 (8.4%) deaths, 155 (25.8%) MVRs, and 39 (6.49%) redo PMVs, accounting for a total of 245 (40.7%) patients with combined events at follow-up. Of the remaining 330 patients who were free of combined events, 312 (95%) were in NYHA class I or II. Follow-up events in patients with Echo-Sc > 8 included 59 (21.2%) deaths, 79 (28.4%) MVRs, and 15 (5.4%) redo PMVs, accounting for a total of 153 (55.03%) patients with combined events at follow-up. Of the remaining 116 patients who were free of any event, 105 (91%) were in NYHA class I or II^[9]. Figures 12, 13, and 14 show the Kaplan-Meier survival and event free survival estimates for all patients, subdivided by patients with Echo-Sc ≤ 8 and > 8 and patients with Echo-Sc ≥ 12 [Figure 14].

Although adverse events (death, mitral valve surgery, and redo PMV) were low within the first 5 years of follow-up, a progressive number of events occurred beyond this period. Nevertheless, survival (82% *vs.* 57%) and event-free survival (57.4% *vs.* 43.1%) at 12-year follow-up was greater in patients with Echo-Sc ≤ 8 compared to patients with Echo-Sc > 8 ($P < 0.0001$). Cox regression analysis identified post-PMV mitral regurgitation \geq grade 3 +, Echo-Sc > 8 , older age, prior surgical commissurotomy, NYHA functional class IV, pre-PMV mitral regurgitation ≥ 2 +, and higher post-PMV pulmonary artery pressure as independent predictors of combined events at long-term follow-up^[9].

PMV VS. SURGICAL COMMISSUROTOMY

Several studies have compared the immediate and early follow-up results of PMV *vs.* open or closed surgical commissurotomy. These initial trials results of PMV *vs.* surgical commissurotomy are encouraging and favor PMV for the treatment of patients with rheumatic mitral stenosis with suitable mitral valve morphology^[10,21-23,47]. Thus, it seems reasonable to recommend PMV for patients with Echo-Sc ≤ 8 , especially if they have other favorable characteristics (age < 45 years, ≤ 2 + MR, and no previous mitral surgery). The question remains as to which procedure, MVR or PMV, is more suitable for patients with Echo-Sc > 8 . A successful PMV result is obtained in 56.4% of these patients, and only 43.1% of them were free of combined events at the 12-year follow-up. Because a good immediate outcome was achieved in 61% of patients with Echo-Sc between 9 and 11 and 39% were free of combined events at 5-year follow-up [Figure 13], PMV might be considered the first choice in these patients if they are free of other risk variables.

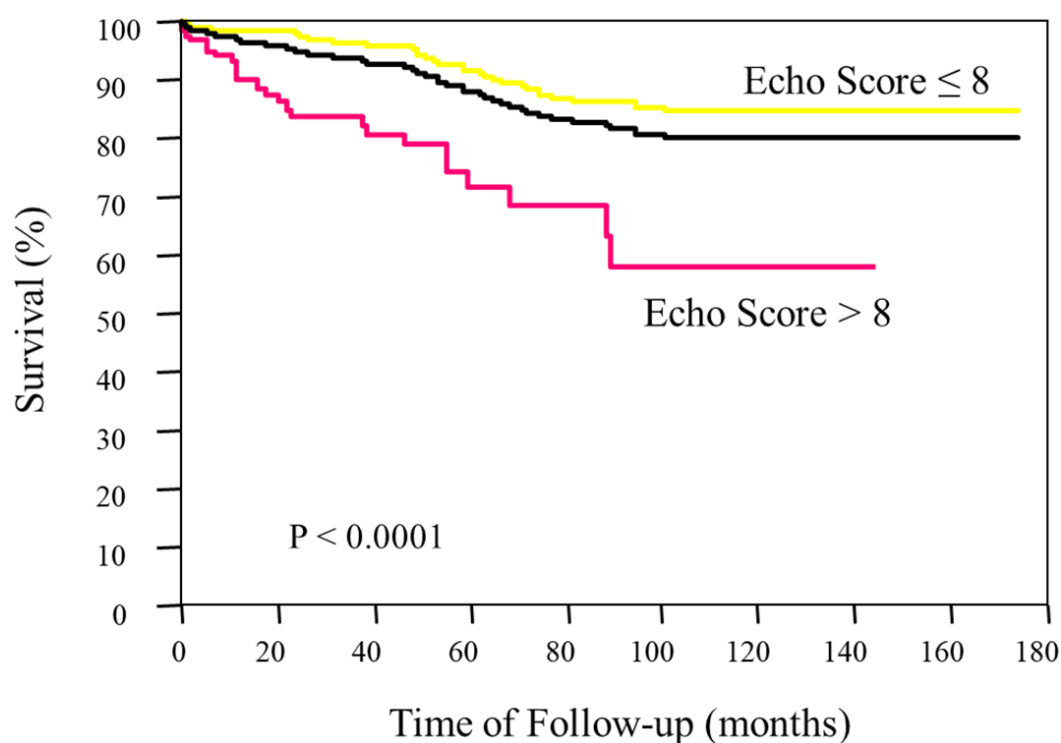


Figure 12. Kaplan-Meier survival estimates for all patients and for patients with Echo-Sc ≤ 8 and > 8 . Modified from Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC. Which patients benefit from percutaneous mitral balloon valvuloplasty? Pre and post-valvuloplasty variables that predict 15-year outcome^[13]

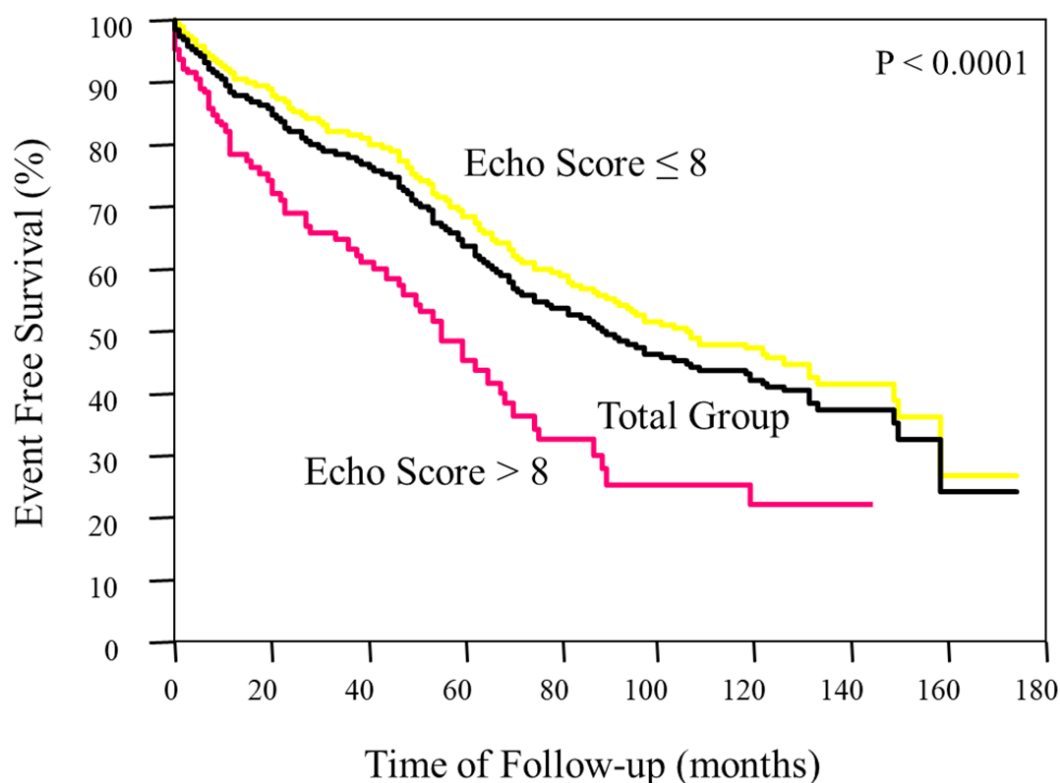


Figure 13. Kaplan-Meier event-free survival estimates (alive and free of MVR or redo PMV) for all patients and for patients with Echo Sc ≤ 8 and > 8 . Modified from Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC. Which patients benefit from percutaneous mitral balloon valvuloplasty? Pre and post -valvuloplasty variables that predict 15-year outcome^[13]. PMV: percutaneous mitral balloon valvuloplasty; MVR: mitral valve replacement

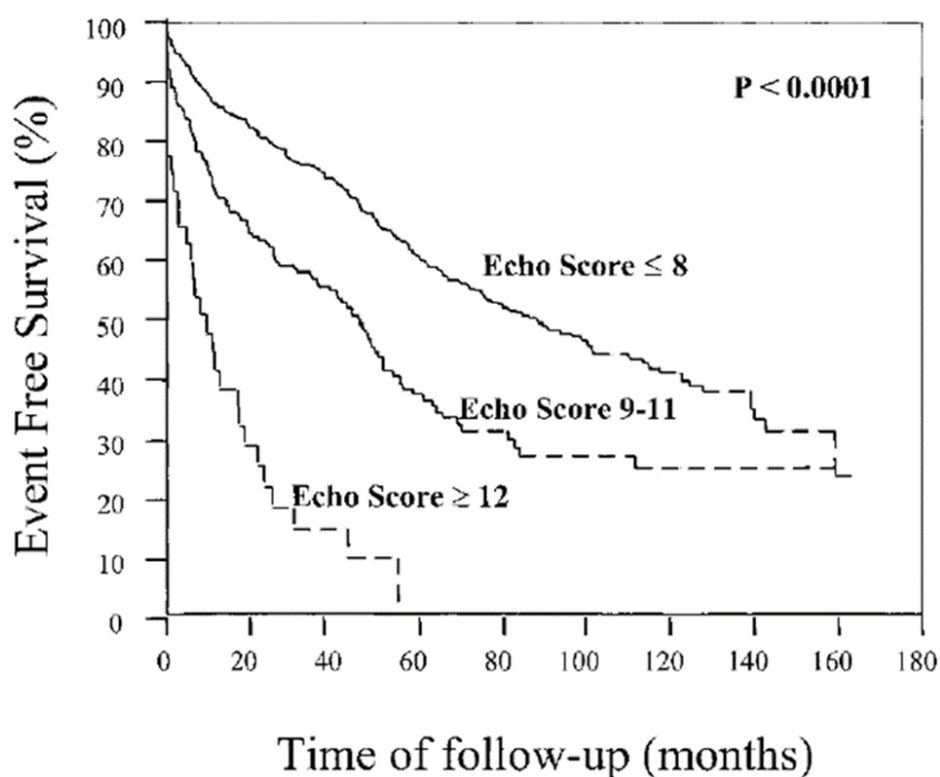


Figure 14. Kaplan-Meier event-free survival estimates (alive and free of MVR or redo PMV) for patients with Echo-Sc ≤ 8 , Echo-Sc 9 to 11, and Echo-Sc ≥ 12 . Modified from Palacios IF, Sanchez PL, Harrell LC, Weyman AE, Block PC. Which patients benefit from percutaneous mitral balloon valvuloplasty? Pre and post-valvuloplasty variables that predict 15-year outcome^[13]. PMV: percutaneous mitral balloon valvuloplasty; MVR: mitral valve replacement

Conversely, patients with Echo-Sc ≥ 12 should be referred for MVR, because only 36% had successful PMV and only 10% were free of events at 4 years post-PMV [Figure 14]. Nevertheless, PMV could be considered as a palliative procedure if the patients are non or very high surgical candidates.

PMV IN PATIENTS WITH PREVIOUS SURGICAL COMMISSUROTOMY

Although the increase in MVA with PMV is inversely related to the presence of previous surgical mitral commissurotomy, PMV can produce a good outcome in this group of patients. The post-PMV mean MVA in 154 patients with previous surgical commissurotomy was $1.8 \pm 0.7 \text{ cm}^2$ compared with an MVA of $1.9 \pm 0.6 \text{ cm}^2$ in patients without previous surgical commissurotomy ($P < 0.05$). In this group of patients, an echocardiographic score ≤ 8 was an important predictor of a successful hemodynamic immediate outcome^[48]. This application for PMV assumes that the mechanism of restenosis after surgical mitral commissurotomy is due to commissural fusion as determined by echocardiography.

REDO PMV IN PATIENTS WITH POST-PMV MITRAL RESTENOSIS

PMV for mitral restenosis is feasible, safe, and achieves immediate and long-term outcome comparable to initial PMV^[49]. We reported the immediate outcome and long-term clinical follow-up results of 36 patients (mean age 58 ± 13 years, 75% women) with symptomatic mitral restenosis after prior PMV, who were treated with a repeat PMV at 34.6 ± 28 months after the initial PMV^[49]. The mean follow-up period was 30 ± 33 months with a maximal follow-up of 10 years. An immediate procedural success was obtained in 75% patients. The overall survival rate was 74%, 72%, and 71% at one, two, and three years, respectively. The event-free survival rate was 61%, 54% and 47% at one, two, and three years, respectively. In the presence

of comorbid diseases (cardiac and noncardiac), the two-year event-free survival was reduced to 29% as compared with 86% in patients without comorbid diseases. Cox regression analysis identified Echo-Score ($P = 0.03$), post-PMV mitral valve area ($P = 0.003$), post-PMV mitral regurgitation grade ($P = 0.02$) and post-PMV pulmonary artery pressure ($P = 0.0001$) as independent predictors of event-free survival after repeat PMV. We concluded that repeat PMV for post-PMV mitral restenosis results in good immediate and long-term outcome, particularly in patients with restenosis due to commissure fusion, low echocardiographic scores, and absence of comorbid diseases. Although the results are less favorable in patients with suboptimal characteristics, repeat PMV has a palliative role if the patients are not or very high surgical candidates^[49].

PMV AND AGE

Sanchez *et al.*^[24] reported the impact of age in the immediate and long-term outcome of PMV. For purpose of analysis, these patients were divided into four age groups: group 1 (≤ 35 years), group 2 (36-55 years), group 3 (56-75 years), and group 4 (> 75 years). The incidence of atrial fibrillation, calcified valves under fluoroscopy, higher echocardiographic score, NYHA class IV, and pre-PMV MR increased with patient's age. As patients became older, a lower post-PMV mitral valve area ($2.1 \pm 0.7 \text{ cm}^2$, $2.0 \pm 0.6 \text{ cm}^2$, $1.8 \pm 0.6 \text{ cm}^2$, and $1.6 \pm 0.6 \text{ cm}^2$; $P < 0.0001$) and progressive decrease in procedural success (81.4%, 80.5%, 65.3%, and 53%; $P < 0.0001$) were observed. Younger age was identified as an independent predictor of PMV success by multiple stepwise logistic regression [odds ratio: 3.33; confidence interval (CI): 1.41-7.69, $P = 0.006$]. Furthermore, age was identified as an independent predictor of long-term events by Cox regression analysis [risk ratio: 1.02; CI: 1.01-1.03, $P < 0.00001$]. However, the effect of age seemed to be blunted by the morphology of the valve at follow-up, as patients with Echo-Sc greater than 8 in groups 2, 3, and 4 presented similar combined event-free survival (death, mitral valve replacement, or redo PMV). They concluded that age is an important predictor of immediate and long-term outcomes after PMV, particularly in patients with optimal mitral valve morphology^[20,24,50].

PMV AND PREGNANCY

Surgical mitral commissurotomy has been performed in pregnant women with severe mitral stenosis. Because the risk of anesthesia and surgery for the mother and the fetus are increased, this operation is reserved for those patients with incapacitating symptoms refractory to medical therapy^[51]. Under these conditions, PMV can be performed safely after the twentieth week of pregnancy with minimal radiation to the fetus^[51,52]. Because of the definite risk in women with severe mitral stenosis of developing symptoms during pregnancy, PMV should be considered when a patient is considering becoming pregnant and has evidence of severe mitral stenosis. Esteves *et al.*^[52] reported that PMV can be performed during pregnancy without significant maternal risk or fetal morbidity or mortality. They report the results of 71 consecutive pregnant women with severe rheumatic mitral stenosis and severe congestive heart failure (New York Heart Association class III and IV) referred for PMV. All patients underwent clinical and obstetric evaluations, electrocardiography, and 2-dimensional and Doppler echocardiography. PMV was successful in all patients, resulting in a significant increase in mitral valve area from $0.9 \pm 0.2 \text{ cm}^2$ to $2.0 \pm 0.3 \text{ cm}^2$ ($P < 0.001$). At the end of pregnancy, 98% of the patients were in New York Heart Association functional class I or II. At a mean follow-up of 44 ± 31 months, the total event-free survival rate was 54%. The mean gestational age at delivery time was 38 ± 1 weeks. Preterm deliveries occurred in 9 patients (13%), including 2 twin pregnancies. The remaining 66 of 75 newborns (88%) had normal weight (mean $2.8 \pm 0.6 \text{ kg}$) at delivery. At long-term follow-up of 44 ± 31 months after birth, the 66 children exhibited normal growth and development and did not show any clinical abnormalities. They concluded that during pregnancy PMV is safe and effective, has a low morbidity and mortality rate for the mother and the fetus, and has favorable long-term results in pregnant women with rheumatic mitral stenosis in New York Heart Association functional class III or IV^[51,52].

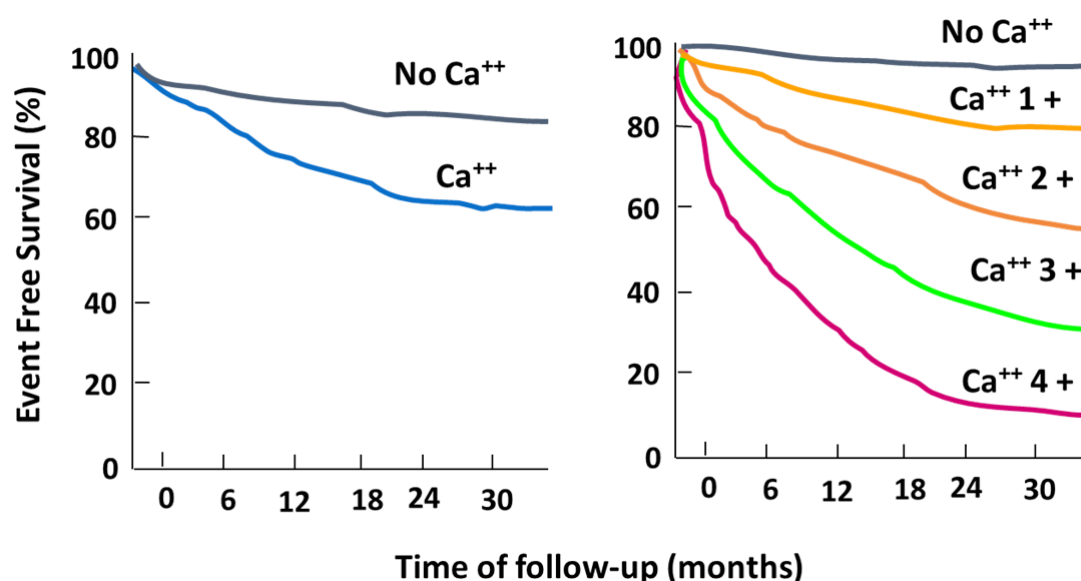


Figure 15. Estimated survival rate at 2 years after percutaneous mitral balloon valvuloplasty, stratified by severity of calcification. Ca 0 to Ca 4+. Modified from Tuzcu EM, Block PC, Griffin B, Dinsmore R, Newell JB, Palacios IF. Percutaneous mitral balloon valvotomy in patients with calcific mitral stenosis: immediate and long-term outcome^[53]

FOLLOW-UP OF PATIENTS WITH CALCIFIED MITRAL VALVES

The presence of fluoroscopically visible calcification on the mitral valve influences the success of PMV. Tuzcu *et al.*^[53] reported that patients with heavily ($\geq 3+$) calcified valves under fluoroscopy have a poorer immediate outcome as reflected in a smaller post-PMV MVA and greater post-PMV mitral valve gradient. Immediate outcome is progressively worse as the calcification becomes more severe. As shown in Figure 15, the long-term results of PMV are significantly different in calcified and uncalcified groups and in subgroups of the calcified group^[53,54]. The estimated 2-year survival is significantly lower for patients with calcified mitral valves than for those with uncalcified valves (80% vs. 99%). The survival curve becomes worse as the severity of valvular calcification becomes more severe. Freedom from mitral valve replacement at 2 years was significantly lower for patients with calcified valves than for those with uncalcified valves (67% vs. 93%). Similarly, the estimated event-free survival at 2 years in the calcified group became significantly poorer as the severity of calcification increased. The estimated event-free survival at 2 years was significantly lower for the calcified than for the uncalcified group (63% vs. 88%). The actuarial survival curves with freedom from combined events at 2 years in the calcified group became significantly poorer as the severity of calcification increased. These findings are in agreement with several follow-up studies of surgical commissurotomy, which demonstrate that patients with calcified mitral valves had a poorer survival compared with those with uncalcified valves^[53,55].

FOLLOW-UP OF PATIENTS WITH ATRIAL FIBRILLATION

Leon *et al.*^[54] reported that the presence of atrial fibrillation is associated with inferior immediate and long-term outcome after PMV as reflected in a smaller post-PMV MVA and a lower event-free survival (freedom from death, redo-PMV, and mitral valve surgery) at a median follow-up time of 61 months (32% vs. 61%; $P < 0.0001$). Analysis of pre-procedural and procedural characteristics revealed that this association is most likely explained by the presence of multiple factors in the atrial fibrillation group that adversely affect the immediate and long-term outcome of PMV. Patients in atrial fibrillation are older and presented more frequently with NYHA class IV, Echo-Sc greater than 8, calcified valves under fluoroscopy, and a history of previous surgical commissurotomy. In the group of patients in atrial fibrillation, the authors identified severe post-PMV MR (> 31) ($P < 0.0001$), echocardiographic score greater than 8 ($P = 0.004$), and pre-

PMV NYHA class IV ($P = 0.046$) as independent predictors of combined events at follow-up. The presence of atrial fibrillation per se should not be the only determinant in the decision process regarding treatment options in patients with rheumatic mitral stenosis. The presence of an Echo-Sc less than or equal to 8 primarily identifies a subgroup of patients in atrial fibrillation in whom percutaneous balloon valvotomy is likely to be successful and provide good long-term results. Therefore, in this group of atrial fibrillation patients, PMV should be the procedure of choice for the treatment of rheumatic mitral stenosis^[54].

PMV IN PATIENTS WITH AORTIC REGURGITATION

Sanchez-Ledesma *et al.*^[56] examine the effect of concomitant aortic regurgitation (AR) on PMV procedural success, short-term, and long-term clinical outcome in 676 procedures performed. Of which, 361 (53.4%) had no AR, 287 (42.5%) mild AR, and 28 (4.1%) moderate AR. There were no differences between groups in the pre-procedure characteristics, procedural success, or in the incidence of in-hospital adverse events. At a median follow-up of 4.11 years, there was no difference in the overall survival rate ($P = 0.22$), MVR rate ($P = 0.69$), or redo PMV incidence ($P = 0.33$). The rate of AVR was higher in the moderate AR group (0.9% vs. 1.9% vs. 13%, $P = 0.003$). Mean time to AVR was 4.5 years and did not differ significantly between patients with no AR, mild AR, or moderate AR (2.9 ± 2.1 vs. $5.7 \pm$ vs. 4.1 ± 2.5 years, $P = 0.46$). They concluded that concomitant AR at the time of PMV does not influence procedural success and is not associated with inferior outcome. A minority of patients with MS and moderate AR who undergo PMV will require subsequent AVR on long-term follow-up. Thus, patients with rheumatic MS and mild to moderate AR remain good candidates for PMV^[56].

THE DOUBLE-BALLOON VS. THE INOUE TECHNIQUES OF PMV

Today the Inoue approach of PMV is the technique more widely used. There was controversy as to whether the double-balloon or the Inoue technique provided superior immediate and long-term results. We compared the immediate procedural and the long-term clinical outcomes after PMV using the double-balloon technique ($n = 659$) and Inoue technique ($n = 233$). There were no statistically significant differences in baseline clinical and morphologic characteristics between the double-balloon technique and Inoue technique patients. Although the post-PMV MVA was larger with the double-balloon technique (1.94 ± 0.72 vs. 1.81 ± 0.58 ; $P < 0.01$), success rate (71.3% vs. 69.1%; $P =$ not significant), incidence of greater than grade 3 + MR (9% vs. 9%), and in-hospital complications were similar. Furthermore, as shown in Figure 16 long-term and event-free survival were similar with both techniques^[57,58]. In conclusion, both the Inoue and the double-balloon techniques are equally effective techniques of PMV. The procedure of choice should be performed based on the interventionist experience with the technique^[57,58].

FOLLOW-UP OF THE BEST PATIENTS

In patients identified as optimal candidates for PMV, this technique results in excellent immediate and long-term outcome. Optimal candidates for PMV are those patients meeting the following characteristics: (1) age 45 years old or younger; (2) normal sinus rhythm; (3) Echo-Sc ≤ 8 ; (4) no history of previous surgical commissurotomy; and (5) pre-PMV MR $\leq 1 +$ Sellers grade^[10,50]. From 879 consecutive patients undergoing PMV at the Massachusetts General Hospital, the authors identified 136 patients with optimal pre-procedure characteristics^[10]. In these patients, PMV results in an 81% success rate and a 3.4% incidence of major in-hospital combined events (death and/or MVR). In these patients, PMV results in a 95% survival and 61% event-free survival at the 12-year follow-up^[10,29,55].

PMV IN PATIENTS WITH PULMONARY ARTERY HYPERTENSION

Patients with mitral stenosis with severe pulmonary hypertension constitute a high-risk subset for surgical commissurotomy or valve replacement. The degree of pulmonary artery hypertension before PMV is inversely related to the immediate and long-term outcome of PMV^[59]. Chen and colleagues divided 564

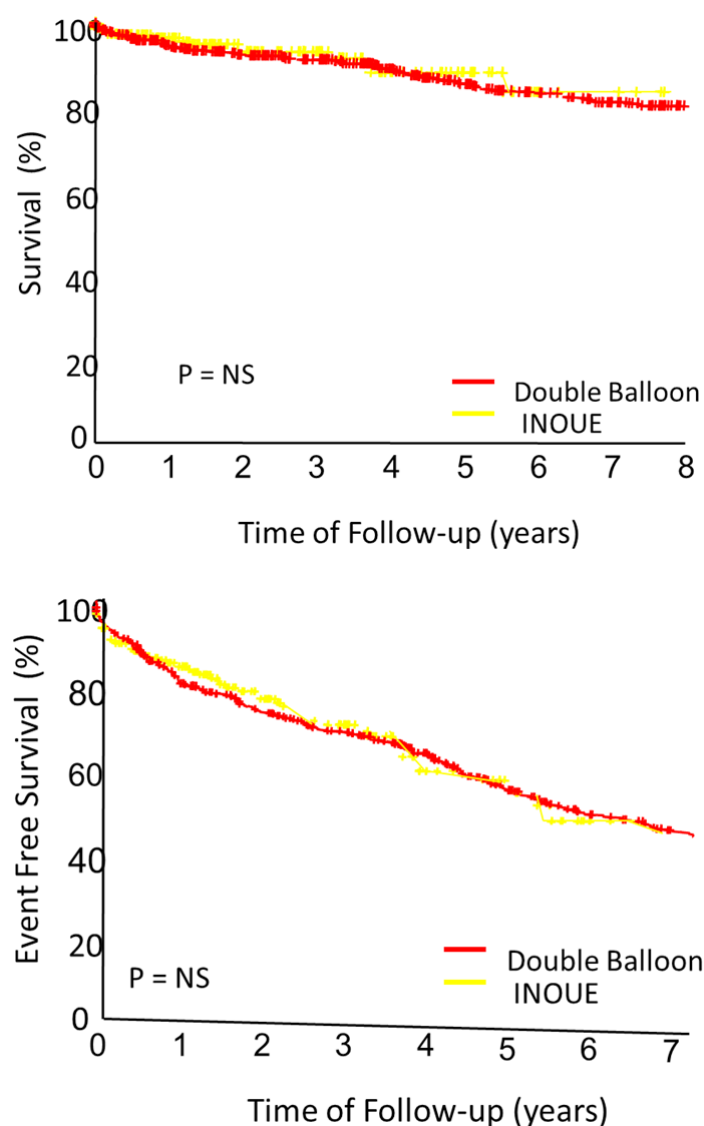


Figure 16. Comparison between the two PMV techniques (Double balloon vs. Inoue balloon) on survival (upper panel) and event-free survival (inferior panel) at long-term follow-up. Modified from Leon MN, Harrell LC, Simosa HF, Mahdi NA, Pathan A, Lopez-Cuellar J, Palacios IF. Comparison of immediate and long-term results of mitral balloon valvotomy with the double balloon vs. Inoue techniques^[60]. PMV: percutaneous mitral balloon valvuloplasty

patients undergoing PMV at Massachusetts General Hospital into 3 groups on the basis of the pulmonary vascular resistance (PVR) obtained at cardiac catheterization immediately before PMV: group I with less than or equal to 250 dynes s.cm^{-5} (normal/mildly elevated resistance) comprised 332 patients (59%), group II with a PVR between 251 and 400 250 dynes s.cm^{-5} (moderately elevated resistance) comprised 110 patients (19.5%), and group III with a PVR greater than or equal to 400 dynes s.cm^{-5} comprised 122 patients (21.5%). Patients in groups I and II were younger and had less severe heart failure symptoms measured by NYHA class and a lower incidence of Echo-Sc less than 8, atrial fibrillation, and calcium noted on fluoroscopy than patients in group III. Before and after PMV, patients with higher PVR had a smaller MVA, lower cardiac output, and higher mean pulmonary artery pressure. For groups I, II, and III patients, the immediate success rates for PMV were 68%, 56%, and 45%, respectively. Therefore, patients in the group with severely elevated pulmonary artery resistance before the procedure had lower immediate success rates of PMV. At long-term follow-up, patients with severely elevated pulmonary vascular resistance had a significant

lower survival and event-free survival (survival with freedom from mitral valve surgery or NYHA class III or IV heart failure). Furthermore, Cruz-Gonzalez *et al.*^[59] examined the effect of elevated PVR on PMV procedural success, short- and long-term clinical outcomes (i.e., mortality, mitral valve surgery, and redo PMV) in 926 consecutive patients undergoing PMV at the Massachusetts General Hospital. Of the 926 patients, 263 (28.4%) had PVR ≥ 4 Woods units (WU) and 663 (71.6%) had PVR < 4 WU. Patients with PVR ≥ 4 WU were older and more symptomatic and had worse valve morphology for PMV. The patients with PVR ≥ 4 WU also had lower PMV procedural success than those with PVR < 4 WU (78.2% vs. 85.6%, $P = 0.006$). However, after multivariate adjustment, PVR was no longer an independent predictor of PMV success nor an independent predictor of the combined end point at a median follow-up of 3.2 years. They concluded that elevated PVR at PMV is not an independent predictor of procedural success or long-term outcomes. Therefore, appropriately selected patients with rheumatic mitral stenosis might benefit from PMV, even in the presence of elevated pre-procedural PVR^[59].

TRANSCATHETER MVR, A FUTURISTIC PROMISING APPROACH

Mitral annulus calcification (MAC) is another disease that could result in severe mitral stenosis or mixed mitral valve disease. Patients with MAC are frequently an elderly high-risk population with multiple comorbidities and a high risk of cardiovascular death and all-cause mortality. The risk of surgical MVR in patients with severe MAC is high. Transcatheter MVR (TMVR) has recently emerged as an exciting new frontier in the field of cardiac structural interventions. Results of the earlier experience with TMVR are encouraging but remain at an early stage^[60,61].

PMV IN PATIENTS WITH STENOSED MITRAL BIOPROSTHESIS

Transcatheter mitral valve-in-valve implantation for dysfunctional biological mitral prosthesis can be performed with minimal operative morbidity and mortality and favorable midterm clinical and hemodynamic outcomes. Nowadays, transcatheter valve in valve has a class IIa indication for bioprosthetic mitral valve degeneration in high-risk to prohibited surgical risk patients according to AHA/ACC 2017 guidelines. However, due to anatomic limitations, not all patients qualify for this procedure and PMV is still an option with symptomatic and hemodynamic benefit. There have been limited reports of successful procedures of balloon valvuloplasty for bioprosthetic mitral valve stenosis. However, there is a need for prospective studies to assess the efficacy and durability of this procedure^[62,63].

CONCLUSION

PMV should be the procedure of choice for the treatment of patients with rheumatic mitral stenosis who are, from clinical and morphologic points of view, optimal candidates for PMV. Patients with Echo-Sc ≤ 8 have the best results, particularly if they are young, are in normal sinus rhythm, have no pulmonary hypertension, and have no evidence of calcification of the mitral valve under fluoroscopy. The immediate and long-term results of PMV in this group of patients are similar to those reported after surgical mitral commissurotomy. Patients with Echo-Sc > 8 have only a 50% chance to obtain a successful hemodynamic result with PMV, and long-term follow-up results are worse than those from patients with Echo-Sc ≤ 8 . In patients with Echo-Sc ≥ 12 , it is unlikely that PMV could produce good immediate or long-term results. They preferably should undergo open heart surgery. PMV could be performed in these patients if they are non- or high-risk surgical candidates. Finally, much remains to be done in refining indications for patients with few or no symptoms and those with unfavorable anatomy. The question remains as to which procedure, MVR or PMV, is more suitable for patients with Echo-Sc > 8 but ≤ 12 (the so called the gray zone). Analysis of the individual component of the Echo-Sc could be helpful in decide to proceed with PMV over surgery. Severity of leaflet thickening and degree of sub valvular disease would favor MVR, while mobility and calcification would favor PMV. Surgical therapy for mitral stenosis should be reserved, for patients who have $\leq 2 +$ Sellers grade of MR by angiography, and for those patients with severe mitral valve

thickening and calcification or with significant sub valvular scarring to warrant mitral valve replacement. Nowadays the evaluation and grading of mitral regurgitation is eminently echocardiographic. Although the distinction between mild and severe grade of mitral regurgitation using echocardiography is easy, it is not the same for the cases of intermediate (II and III) grades. Doppler echocardiography is dependent on hemodynamic parameters such as the preload, afterload, and rhythm, anatomic parameters such as the dimensions of left atrium, technical parameters such as the “window”, and operator’s experience. Thus, echocardiographic evaluation of mitral regurgitation severity should be done using an integrative approach that incorporates multiple parameters, including semi-quantitative measures (vena contracta width or area) and quantitative measures (effective regurgitant orifice area, regurgitant volume, and regurgitant fraction).

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The author contributed solely to the article.

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Original Article

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Parenchymal transection in robotic liver resection: results of 70 resections using the Vessel Sealer

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Abstract

Aim: There is no standard technique for transection of the hepatic parenchyma during robotic liver resection. The aim of this study was to describe the outcomes of robotic liver resections using the Vessel Sealer for parenchymal transection.

Methods: This is a *post hoc* analysis of a prospective database. All consecutive patients who underwent robotic liver resection in the Regional Academic Cancer Centre, Utrecht, Netherlands, between August 2015 and January 2019 were included.

Results: A total of 70 robotic liver resections were performed, including 60 minor resections (86%) and ten hemihepatectomies (14%). Five procedures (7%) were converted. Mean parenchymal transection time was 43 ± 26 min. Median blood loss was 150 mL (interquartile range 40-300). Ten patients (14%) suffered from a major complication, and three patients (4%) had bile leakage postoperatively. One patient died from post-hepatectomy liver failure.

Conclusion: Based on the results of this series, consisting of 60 minor liver resections and 10 hemihepatectomies, we conclude that the use of the Vessel Sealer during the parenchymal transection in liver resection is feasible and safe.



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Keywords: Robotic liver resection, minimally-invasive hepatectomy, robot-assisted surgery, robotic surgery, hepatic resection

INTRODUCTION

The benefits to the patient of a minimally invasive approach to liver resection include fewer complications, less blood loss, and an enhanced recovery after surgery^[1]. Conventional laparoscopy, however, has technical limitations. Laparoscopic instruments have a straight work-axis and, therefore, have limited freedom of movement. To overcome these impairments the surgical robot was introduced, which provides articulating instruments, a 3-dimensional view, and scaled movements^[2,3]. Several studies have shown the safety and feasibility of robotic liver resection^[4].

During liver resection, transection of the hepatic parenchyma forms an essential part of the procedure. Inadequate sealing of vascular and biliary structures can result in bile leakage or bleeding, potentially causing postoperative complications and mortality. Several techniques and devices have been developed for parenchymal transection, such as the clamp crushing technique, cavitron ultrasonic surgical aspirator (CUSA) (Integra LifeSciences, Tullamore, Ireland), ultrasonic devices, staplers and mono- and bipolar devices^[5,6]. Most of these techniques were developed for, and are predominantly used in, open surgery. In laparoscopic liver surgery, the transection is mostly performed using CUSA, sealing devices and staplers. For robotic surgery, it has not yet been determined which device is best suited for parenchymal transection. Currently, the robotic Harmonic Scalpel (Intuitive Surgical, Sunnyvale, California, USA) or robotic bipolar cautery (Maryland Bipolar Forceps, Intuitive Surgical, Sunnyvale, California, USA) are the most frequently reported devices used for parenchymal transection during robotic liver resection^[7]. However, the robotic Harmonic Scalpel lacks the ability to articulate and the Maryland Bipolar Forceps seems not optimally suited for larger transection planes.

The EndoWrist® One™ Vessel Sealer (on the Xi/X robotic systems: EndoWrist® One™ Vessel Sealer Extend) (Intuitive Surgical Inc., Sunnyvale, CA, USA) is a fully wristed robotic energy device (60° of articulation in all directions for the Extend) that is approved to seal and cut vessels up to 7 mm in diameter. The aim of this study is to report the technical details and clinical outcomes of a series of consecutive robotic liver resections during which the Vessel Sealer was used for parenchymal transection.

METHODS

Study design

This is a *post hoc* analysis of a prospective database. In addition, recordings of the surgical procedures were reviewed retrospectively for determination of parenchymal transection duration. All consecutive patients who underwent robotic liver resection in the Regional Academic Cancer Centre Utrecht (RAKU) at both University Medical Centre Utrecht and St. Antonius Hospital Nieuwegein, between 1st August 2015 and 11th January 2019, were included. Patients were selected for robotic liver resection in a multidisciplinary board meeting. As this case series also reflects a learning curve of robotic hepatectomy starting with easy minor resections and progressing to difficultly-located minor resections, and eventually hemihepatectomy, no uniform inclusion criteria are applicable. In general, exclusion criteria for the robotic approach in this series were extended liver resection (> 4 segments), tumour adjacent to the inferior vena cava or hepatic vein insertions, and perihilar cholangiocarcinoma. In the first cases, cirrhosis was a relative contraindication (unless minor/wedge resection) but, with growing experience, this was no longer considered a contraindication.

We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement^[8]. Eleven of the minor resections of the posterosuperior liver segments have been described previously within a multi-institutional cohort study^[9]. The overall initial experience at our centre has been published previously, including surgical outcomes of the first eighteen procedures^[3,10].

Definitions

Liver segments were defined using Couinaud's classification^[11]. Segments 2, 3, 4B, 5 and 6 were classified as anterolateral segments; segments 1, 4A, 7 and 8 were classified as posterosuperior segments. Minor liver resection was defined as the resection of three or less segments, while major liver resection was defined as the resection of four or more segments. A wedge resection was counted as a half segment^[12]. En-bloc resections of the adrenal gland or diaphragm and cholecystectomies were not considered concomitant procedures. Operative time was defined as time from first incision until wound closure. Postoperative complications were scored using the Clavien-Dindo (CD) grading system for postoperative complications^[13]. Major complications were defined as CD grade III or higher. Bile leak was defined using the International Study Group of Liver Surgery definition and grading system^[14]. Complications were scored during index admission. If a patient was readmitted within ten days after discharge, this readmission was still considered index admission. Conversion was defined as a laparotomy made for any reason other than for specimen extraction. Resections were considered radical (R0) if no tumour cells were present in the transection surface and within 1 mm of the transection surface. Resections were considered irradical (R1) if tumour cells were present in the transection surface or within 1 mm of the transection surface^[15]. If multiple tumours were resected, the closest margin determined the R status.

Data collection

The baseline patient characteristics collected were the year of surgery, age, sex, body mass index, American Society of Anesthesiologists score, previous abdominal surgery, and indication for resection. Data on details of the operation collected included the resection performed, concomitant procedures, operative time, console time, parenchymal transection time, estimated blood loss, conversion, placement of surgical drain, use of Pringle manoeuvre, duration of inflow occlusion, epidural analgesia, number of stapler loads used per procedure, type of robotic system, definitive histopathological diagnosis, margin status, and tumour size. Postoperative outcomes were CD grade III or higher complications, bile leakage, unplanned ICU admission, relaparotomy, percutaneous or endoscopic catheter drainage, length of hospital stay, readmission, 30-day mortality, 90-day mortality and trocar herniation during 1-year follow-up.

Comparison with conventional laparoscopic approach

Additionally, to put our results into perspective and to compare outcomes of our series of robotic liver resections to conventional laparoscopy, we have provided an overview of the outcomes of all laparoscopic liver resections performed in the Netherlands between 2011 and 2016. Data were extracted from the Dutch nationwide LAELIVE database on minimally invasive liver surgery^[16] (published in part).

Statistical analysis

Data with a normal distribution were reported as mean with standard deviation (SD). Data with a skewed distribution were reported as median with interquartile range (IQR). Missing values were reported for each parameter.

Ethical approval

The Medical Ethics Review Committee approved the study protocol with a waiver for informed consent.

Parenchymal transection technique

In the majority of procedures, parenchymal transection began with ultrasound for delineation of the oncological margin. Either a laparoscopic ultrasound probe was used or a robotic 'drop-in' probe (both:

Table 1. Patient characteristics

Parameter	Outcome
Year of surgery, <i>n</i> (%)	
2014	3 (4)
2015	9 (13)
2016	9 (13)
2017	19 (27)
2018	28 (40)
2019 (up to January 11th)	2 (3)
Age, mean (SD), years	60 (14)
Sex, male, <i>n</i> (%)	35 (50)
BMI, mean (SD), kg/m ²	27 (5)
ASA score, <i>n</i> (%) ¹	
ASA 1	3 (4)
ASA 2	49 (70)
ASA 3	16 (23)
Previous abdominal surgery, <i>n</i> (%)	45 (64)
Redo liver resection, <i>n</i> (%)	6 (9)
Indication for resection, <i>n</i> (%)	
CRLM	32 (46)
Metastases, other	7 (10)
HCC	16 (23)
Cholangiocarcinoma	5 (7)
Other	10 (14)

¹Two missing values. SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists; CRLM: colorectal liver metastases; HCC: hepatocellular carcinoma

Hitachi Aloka Medical Inc., Wallingford, CT, USA). The latter provides more freedom of movement and hence facilitates imaging of the posterosuperior segments more easily. A Pringle manoeuvre was applied when deemed appropriate. The Vessel Sealer (Extend) was combined with the Maryland Bipolar Forceps and Fenestrated Bipolar Forceps. The Vessel Sealer was employed by clamp-crushing thin layers of tissue (as much as possible under direct vision to avoid lacerations of small veins and bile ducts) with subsequent double sealing and cutting, working in layers from superficial to deep in the liver parenchyma as shown previously^[17,18]. Hem-o-lok clips (Teleflex Inc., Morrisville, NC, USA) or laparoscopic Endo GIA (Medtronic, Minneapolis, MN, USA) were used for control of the hepatic pedicles and larger branches of the hepatic veins, where appropriate.

RESULTS

In total, 70 resections were performed in 68 patients. Two patients underwent robotic liver resection twice for recurrent hepatocellular carcinoma.

Patient characteristics

Patient characteristics are summarized in Table 1. The majority of liver resections was performed for colorectal liver metastases (*n* = 32; 46%).

Operative characteristics and histopathological outcomes

Details on the surgical procedures and pathology are provided in Table 2. Five procedures were converted to laparotomy, for several reasons: in three cases there was a lack of anatomical overview during transection of the hepatic parenchyma; one patient had severe intra-abdominal adhesions; and in one patient a safe oncological margin could not be assured robotically.

In all procedures the Vessel Sealer was used for parenchymal transection. In 22 procedures (31%) stapling devices were also used to control the hepatic pedicles; these resections were left lateral sectionectomies

Table 2. Operative characteristics and histopathological outcomes

Parameter	Outcome
Resections performed, <i>n</i> (%)	
Minor resection solely including anterolateral segments	32 (46)
Wedge resection	17 (24)
Segmental resection	15 (21)
Minor resection including posterosuperior segments	28 (40)
Wedge resection	21 (30)
Segmental resection	7 (10)
Major resection (right and left hepatectomy)	10 (14)
Surgical details	
Concomitant procedures, <i>n</i> (%)	7 (10)
Operative time, mean (SD), min ^{1,^}	160 (78)
Console time, mean (SD), min ^{2,*}	111 (69)
Parenchymal transection time, mean (SD), min ^{3,*}	43 (26)
EBL, median (IQR), mL	150 (40-300)
RBC transfusions, median (IQR)	0 (0-0)
FFP transfusions, median (IQR)	0 (0-0)
Conversion to laparotomy, <i>n</i> (%)	5 (7)
Placement of surgical drain, <i>n</i> (%)	27 (38)
Use of biological agents (TachoSil, Surgicel), <i>n</i> (%) [*]	51 (79)
Pringle manoeuvre performed (intermittent clamping), <i>n</i> (%)	31 (44)
Duration of inflow occlusion, mean (SD) min ¹	41 (15)
Epidural analgesia, <i>n</i> (%)	20 (29)
Stapler loads used per procedure, median (IQR) [*]	0 (0-2)
Robotic system used, <i>n</i> (%)	
da Vinci Si surgical system	55 (79)
da Vinci X surgical system	6 (9)
da Vinci Xi surgical system	9 (13)
Histopathological outcomes, <i>n</i> (%)	
Definitive diagnosis	
CRLM	31 (44)
Metastases, other	5 (7)
HCC	15 (21)
Intrahepatic Cholangiocarcinoma	4 (6)
Benign	13 (19)
Other	2 (3)
Cirrhosis on final pathology, <i>n</i> (%)	8 (11)
Radical (R0) resection [#]	42 (76)
Tumor size, mean (SD), mm [§]	37 (26)

¹One missing value; ²four missing values; ³twenty missing values; [^]operative time for liver resection, corrected for concomitant procedures; ^{*}converted cases excluded; [#]solely reported for malignancies; [§]in cases of multiple resected tumours, only the largest tumour was included in the calculation. SD: standard deviation; IQR: interquartile range; RBC: red blood cells; FFP: fresh frozen plasma; CRLM: colorectal liver metastases; HCC: hepatocellular carcinoma; EBL: estimated blood loss

(*n* = 8), left or right hepatectomies (*n* = 8), resections of the posterior sector (*n* = 3), and resections of segment 7 or 8 (*n* = 3). Overall, median blood loss was 150 mL (IQR 40-300), and in 51 procedures (79%) biological agents were applied to the resection surface to ensure haemostasis and biliostasis when deemed appropriate. No technical errors or handling difficulties of the Vessel Sealer were encountered.

Postoperative outcomes

Postoperative outcomes are summarized in Table 3. Ten patients (14%) suffered from a major complication. Three patients (4%) suffered from bile leakage postoperatively, two of which underwent a left hepatectomy, and the third patient underwent a segmental resection of segment 5. Of the three patients who suffered from bile leakage, two patients needed additional radiological drainage. The median length of hospital stay was four days. In total, 37 patients (53%) were discharged on day 4 or earlier; 12 patients (17%) went home on postoperative day one or two.

Table 3. Postoperative outcomes

Parameter	Outcome
Major complication, <i>n</i> (%)	10 (14)
Clavien-Dindo grade III a/b	7 (10)
Non-bilious fluid collection, drained radiologically	2 (3)
Non-bilious fluid collection, drained laparoscopically	1 (1)
Herniated omentum, closed under local anesthesia	1 (1)
Bilious fluid collection, drained radiologically	2 (3)
Trocar herniation, corrected surgically	1 (1)
Clavien-Dindo grade IV a/b	2 (3)
ICU admission for respiratory insufficiency	2 (3)
Bile leakage, <i>n</i> (%)	3 (4)
Grade A	1 (1)
Grade B	2 (3)
ICU admission, <i>n</i> (%)	5 (7)
Unplanned ICU admission, <i>n</i> (%)	3 (4)
Relaparotomies, <i>n</i> (%)	0 (0)
Minimally invasive drainages, <i>n</i> (%)	5 (7)
Length of stay, median (IQR), days	4 (3-6)
Readmission within 10 days, <i>n</i> (%)	4 (6)
Readmission within 90 days, <i>n</i> (%)	6 (9)
30-day mortality, <i>n</i> (%)	1 (1)
90-day mortality, <i>n</i> (%)	1 (1)
Trocar herniation within one year after surgery requiring surgical intervention, <i>n</i> (%)	2 (3)

ICU: intensive care unit; IQR: interquartile range

One patient died postoperatively due to post hepatectomy liver failure. The patient had a past medical history of hepatitis B, no signs of cirrhosis or portal hypertension in preoperative hepatology evaluation, and underwent right hepatectomy for a hepatocellular carcinoma. Due to the lack of anatomical overview during parenchymal transection, the procedure was converted to open hemihepatectomy. Postoperatively, the patient suffered from grade C posthepatectomy liver failure progressing to multiple organ failure and death on postoperative day 12. Definitive pathology showed a hepatocellular carcinoma as well as liver cirrhosis.

Comparison to conventional laparoscopy

A summary of several outcomes from our series and an overview of the outcomes of all laparoscopic liver resections performed in the Netherlands between 2011 and 2016 are provided in Table 4. In total, 885 conventional laparoscopic liver resections were performed, of which 683 (77%) were minor resections. Mean operative time was 164 min (SD 95) for the conventional laparoscopic liver resections and median blood loss was 200 mL (IQR 50-500). A total of 121 procedures (14%) were converted to laparotomy and 76 patients (9%) suffered from a major complication. Nine patients (1%) died after conventional laparoscopic liver resection. Outcomes of our robotic liver resections are comparable to the outcomes of all conventional laparoscopic liver resections performed between 2011 and 2016 in the Netherlands.

DISCUSSION

In this study we report the surgical details and clinical outcomes of 70 consecutive robotic liver resections in which the Vessel Sealer was used for parenchymal transection. Our results demonstrate that the use of this device facilitates safe transection of the hepatic parenchyma, without compromising postoperative clinical outcomes. No postoperative bleeding occurred and only three patients (4%) suffered from bile leakage postoperatively.

Over the past decade, robotic surgery has become an important alternative to conventional laparoscopy. Recently, a nationwide trend in the US towards an increase of the use of robotic surgery has been observed

Table 4. Summarized comparison of robotic liver resection with conventional laparoscopic liver resection

Approach	n	Minor resections, n (%)	Operative time, mean (SD), min	Blood loss, median (IQR), mL	Conversion, n (%)	Major complications, n (%)	Mortality, n (%)
Conventional laparoscopy	885	683 (77)*	164 (95)	200 (50-500)	121 (14)	76 (9)	9 (1)
Robotic liver resection	70	60 (86)	160 (78)	150 (40-300)	5 (7)	10 (14)	1 (1)

*Defined as less than three liver segments in Dutch LAELIVE database; ^defined using the Accordion severity grading system of surgical complications. SD: standard deviation; IQR: interquartile range

for pancreatoduodenectomy, whilst the number of conventional laparoscopic pancreatoduodenectomies performed decreased^[19]. This finding supports the hypothesis that robotic surgery might be better suited (and more widely implemented) than conventional laparoscopy for complex procedures, such as pancreatic resection or liver resection.

Since the use of robotic technology in liver resection is gaining momentum, new techniques and devices for parenchymal transection have emerged. Initial series on robotic liver resection mostly reported the use of the robotic Harmonic Scalpel or the Maryland Bipolar Forceps for transection of the parenchyma^[7]. Other currently available devices include the PK Dissecting Forceps (Intuitive Surgical, Sunnyvale, California, USA), EndoClips, robotic stapler, and the Vessel Sealer^[20]. The Harmonic Scalpel, however, lacks the ability to articulate. The Maryland Bipolar Forceps and the PK Dissecting Forceps provide meticulous dissection, but these instruments appear inefficient for larger transection planes. EndoClips provide reliable ligation of vessels and bile ducts, though do not seem efficient for larger transection planes. Robotic staplers facilitate reliable sealing, but are expensive. A few cases using the Vessel Sealer for transection of the parenchyma during robotic liver resection have been reported by Kingham *et al.*^[21], however, no separate outcomes were reported for the different transection techniques used in this study.

The results in our study demonstrate that the use of the Vessel Sealer is feasible and safe during robotic liver resection. Only ten patients (14%) suffered from a major complication, from which one patient died. However, this patient suffered from post hepatectomy liver failure, which is most likely a consequence of the extent of the resection rather than of the parenchymal transection technique chosen. Three patients (4%) suffered postoperatively from bile leakage, which is comparable to large series reporting on open and laparoscopic liver resection^[22-25]. We could generally employ the Vessel Sealer for parenchymal bile ducts, portal branches and veins but use a stapler and/or hemoclips for inflow/outflow pedicles, major veins, or when larger vascular structures are encountered that are clearly beyond a size that could easily be sealed with a margin within the length of sealer's surface at 90 degrees. We therefore conclude that the Vessel Sealer is appropriate to seal most vascular structures encountered within the parenchyma of the liver segments. The R1 resection rate in our series (defined as a surgical margin of < 1 mm) appears to be relatively high (24%). However, studies show that R1 resection for colorectal liver metastases (CLRM) can be considered acceptable^[26,27]. The majority of our R1 resections were for CLRM. In addition, in our initial series, robotic manipulation of the liver tissue during resection may have caused inadvertent laceration in the specimen contributing to the number of R1 margins on final pathology in several cases.

Secondly, we provided an overview of all conventional laparoscopic liver resections performed in the Netherlands. Our outcomes are not inferior to those of conventional laparoscopic liver resection. Major morbidity appeared to be lower after conventional laparoscopic liver resection, however, different definitions were used for the grading of the postoperative complications.

Several limitations must be considered for this study. Firstly, the patients who underwent robotic liver resection in this study were selected. Patients with tumours adjacent to the hepatic vessels, patients who

underwent extended hepatectomies (> 4 segments), or patients who had a past medical history of extensive abdominal surgery, were in general not deemed fit for a robotic approach. Although our resections might not fully represent the entire spectrum of liver resections, there were ten major resections performed (14%) and indications varied widely, including patients with cirrhosis (11%). Moreover, 45 patients (64%) were selected who underwent previous abdominal surgery, including previous liver surgery in 6 patients. Second, some surgeons consider the tip of the Vessel Sealer to be too bulky and prefer a more refined instrument for transection of the parenchyma and dissecting out hepatic structures. The updated version of the Vessel Sealer, the Vessel Sealer Extend, however, has a slimmer jaw profile and therefore allows for more delicate dissection. Third, the retrospective nature of the study holds an inherent risk of bias. The comparison we conducted with conventional laparoscopy is obviously weaker than a head-to-head comparison. However, since the outcomes of all laparoscopic liver resections performed in the Netherlands are provided, these results reflect the true outcomes after conventional laparoscopic liver resection.

Based on the results of this series, consisting of 60 minor liver resections and 10 hemihepatectomies, we conclude that the use of the Vessel Sealer during the parenchymal transection in liver resection is feasible and safe.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the design of the work, the data acquisition and analysis, and drafting of the manuscript: Nota CL, Molenaar IQ, te Riele WW, van Santvoort HC, Borel Rinkes IHM, Hagendoorn J

Availability of data and materials

Data are extracted from a prospectively maintained, secured institutional database. Due to the institution's privacy regulation, raw data won't be shared online.

Financial support and sponsorship

None.

Conflicts of interest

Prof. Dr. I. Quintus Molenaar and Dr. Jeroen Hagendoorn are proctor for Intuitive Surgical (Intuitive Surgical Inc., Sunnyvale, CA, USA). The content of this study is solely the responsibility of the authors and does not necessarily represent the official views of Intuitive Surgical. All other authors have declared no conflict of interest.

Ethical approval and consent to participate

Data were extracted from an anonymized database. Hence the study was waived from informed consent.

Consent for publication

Not applicable.

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Review

Open Access



The role of Vitom-3D in the management of spinal meningiomas: review of the literature and illustrative case

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Abstract

The favorable outcome generally associated with spinal meningioma surgery is the result of the continuing refinement of the surgical technique, the use of intraoperative neuromonitoring, and a better understanding of the tumor biological behavior. Among all the technological advancements, visualization tools are the keys to any successful surgical procedure. The operating microscope is the gold standard in all neurosurgical procedures. In recent years, high-definition exoscope systems have entered the field of neurosurgery, as another tool in the armamentarium of the contemporary neurosurgeon. After initial experiences and technical improvements, the exoscope has proven to be best suited for spinal procedures. This study aims to briefly review the exoscope journey in neurosurgery, with a special focus on spinal meningioma surgery. Benefits and limitations are analyzed and an illustrative case is reported. Spinal meningiomas removal under exoscope visualization has proven to be feasible, efficient, and safe. Indication for the use of the exoscope greatly depends on meningioma size, consistency, relationship to surrounding neurovascular structures, and the surgeon's experience. Switching to the operating microscope, if deemed safer, should always be considered.

Keywords: Ergonomics, exoscope, feasible, illumination, magnification, safe, teaching



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INTRODUCTION

Spinal meningiomas are intradural extra-medullary lesions that arise from meningotheelial arachnoid cells within the spinal dura mater. They are the second most common intradural spine tumor, after neuromas, accounting for two-thirds of all intraspinal neoplasms. Surgical treatment of spinal meningiomas is associated with a favorable outcome, both in terms of progression-free survival rate and patients' neurological post-operative status. Improvements in spinal meningiomas surgery are the results of the continuing refinement of the surgical technique, the use of intraoperative neuromonitoring, and a better understanding of meningiomas biological behavior^[1-4]. Spinal meningiomas have shown to be less likely to recur than their intracranial analogs, with the majority of series reporting no significant difference in recurrence rates between Simpson grade I and grade II resections^[5]. The negligible oncological benefit of an aggressive surgical strategy that includes a wide removal of the dural attachment does not seem to outweigh the risk of surgical complications and patients' morbidity, especially for ventral and lateral spinal meningiomas. For this reason, there has been an attitude shift toward less aggressive resections, with the goal of minimizing morbidity^[6-9]. The safety of meningiomas surgery is increased by the use of multimodal neuromonitoring: somatosensory-evoked potentials, motor evoked potentials, and D-waves provide the opportunity to assess the functional integrity of the spinal cord during surgery, bearing the risk of neurological complications. Therefore, intraoperative neuromonitoring adds to the modern treatment of spinal tumors and should be performed in spinal meningiomas surgery^[10].

Among all the technological advances, visualization, magnification, and the illumination of the surgical field are the keys to any successful surgical procedure. After few years from the introduction of the operating microscope by Yasargil and Krayenbuhl in the 1970s^[11], Caspar demonstrated its usefulness for spinal surgery^[12]: the advent of the operating microscope in spinal procedures brought terrific improvement in terms of outcomes^[13-16]. Since then, visualization tools have continued to evolve, along with the inexhaustible research of less invasive surgical techniques to address cranial and spinal pathologies. In the late 1990s, neurosurgeons began to use the endoscope, as a primary visualization tool or in assistance to the microscope. Neuroendoscopy found its best application in skull base approaches and intraventricular surgery^[17-21], while reports of endoscopic spinal surgery remain rather sparse in the literature^[9]. In recent years, high-definition exoscope systems have entered the field of neurosurgery, as another tool in the armamentarium of the contemporary neurosurgeon^[22]. Following preliminary convincing experiences with the exoscope and subsequent technical refinements, reports of application of this device in the setting of more complex cranial and spinal procedures have appeared in the literature^[23-27]. Advantages and disadvantages of the exoscope over the well-established visualization tools, i.e., the operating microscope or endoscope, and the surgical settings in which it could be best indicated still need to be fully elucidated. This article aims to provide a cogent review of the exoscope journey in neurosurgery, with a special focus on spinal procedures and spinal meningioma surgery.

EXOSCOPE IN NEUROSURGERY

During the last three decades, telescopes have been recognized as a valid visualization tool in many surgical fields. The telescope optical system is attached to a high-quality television camera and the surgeon operates by visualizing the anatomic structures and instruments from a video monitor screen placed at an optimal distance. Typical telescopes have very short focal distances and must therefore be introduced directly into the body cavity. Because the lens sits within the body, these devices are usually referred to as endoscopes. Endoscopic visualization in neurosurgery finds its main indication for the treatment of intraventricular lesions and skull base surgery^[17-19,28]. Exoscopes are telescope-based visualization tools that produce very high-quality video images with large focal distance and wide field of view. One of the advantages of the exoscope over the existing telescopes is that the exoscopes are positioned far away from the surgical field, at a distance of approximately 25 to 30 cm. Distinctly from the endoscopic technique, exoscope facilitates the passage of instruments under the scope and does not require dedicated instrumentation.

In 2008, Mamelak *et al.*^[22] reported the initial use of this novel tool in an animal model. The initial impression was that the exoscope had the potential for widespread application for human microsurgical procedures owing adequate image resolution, magnification, and easy and intuitive manipulation. Soon after the initial report, its clinical use has been tested in many surgical disciplines including vascular and cardiac surgery, ENT, hepatic surgery, and neurosurgery^[23,26,29-34]. The outstanding quality of images was largely confirmed and the exoscope earned the right to be seen as another visualization tool in the armamentarium of the contemporary neurosurgeon. The first clinical series of patients undergoing surgery with the aim of the exoscope consisted of technically less demanding neurosurgical procedures for which it was felt that trial use of this device could not potentially affect surgical outcomes. That lack of 3D visualization was a concern to many surgeons and this drawback was mentioned frequently in preliminary studies^[24,35-38]. It took about nine years to further evolve the 2D visualization and introduce the first 3D exoscopic visualization system^[39,40]. In the following years, the 3D exoscope has been used to perform various technical more demanding neurosurgical procedures, even in pediatric cases, including treatment of cerebrovascular disorders (i.e., aneurysm clipping and bypass surgery), degenerative spinal disorders, and resection of cranial and spinal tumors^[41-50].

VITOM®-3D (Video Telescopic Operating Microscope, Karl Storz GmbH & Co. KG, Tuttlingen, Germany), provides a 3D visualization in ultra-high definition (4K) quality, with a focal length of 20-50 mm and magnification ranges from 8× to 30×. It consists of four main parts: the VITOM®-3D camera with integrated illuminator, the IMAGE 1 PILOT control unit, the IMAGE 1 S camera system, and the 3D-monitor. The VITOM®-3D is fixed with a movable holding arm and the camera with an integrated illuminator is placed directly above the operation field at a distance of 25-30 cm. The camera and control unit is connected to the IMAGE 1 S camera system. The 3D-monitor is placed about 1.5 to 2.0 meters distance in front of the surgeon. Ideally, the surgical team (surgeon, assistant, scrub nurse) can equally watch the surgical field on the 3D-monitor by wearing polarized glasses.

The principle features of Vitom-3D allow working in a comfortable setting that is similar to endoscopic surgeries, with the optical advantages of the operating microscope [Figure 1].

The operating microscope is the gold-standard for visualization in neurosurgery^[13,14,16]. However, it has several drawbacks: the cost, which might be up to 500.000 euros; the size, which might be a problem for the intraoperative set up in smaller operating theatres; the surgeon's posture that, depending on the personal height and the angle of the microscope at the surgical field, can result uncomfortable and affect the level of concentration in longer procedures. Finally, the monitor might not be always visible for the scrub nurse during intraoperative positioning. Offering the condition of visualizing the surgical field from a video monitor, both the exoscope and the endoscope require eyes-hands coordination that is different from the operating microscope. Looking and following more easily and immediately involve the operation on a screen, all the staff in the operating theater is more involved in the surgical work. Hence, the exoscope enables the trainees to benefit from a real-time step-by-step surgical learning experience.

The published literature reveals the increased interest in the application of exoscopic visualization in neurosurgery, with the vast majority of articles being published within the last two years^[46,48,49,51-55]. Thanks to literature contributions, it became possible to analyze the advantages and limitations of Vitom-3D. Initial impressions were that the most obvious and clinically relevant benefits are related to working ergonomics (intuitive operating room setup, instrument handling, and surgeons' comfort) and trainees' learning experience. Some disadvantages such as headache, dizziness, and nausea due to wearing polarized glasses, the use of two monitors in selected cases where the surgeon and the assistant were positioned on the opposite side of the patient's body, and the inability to rotate the onscreen picture has been reported as well^[39-41]. The main limitation of the Vitom-3D is the reduced illumination and magnification in the

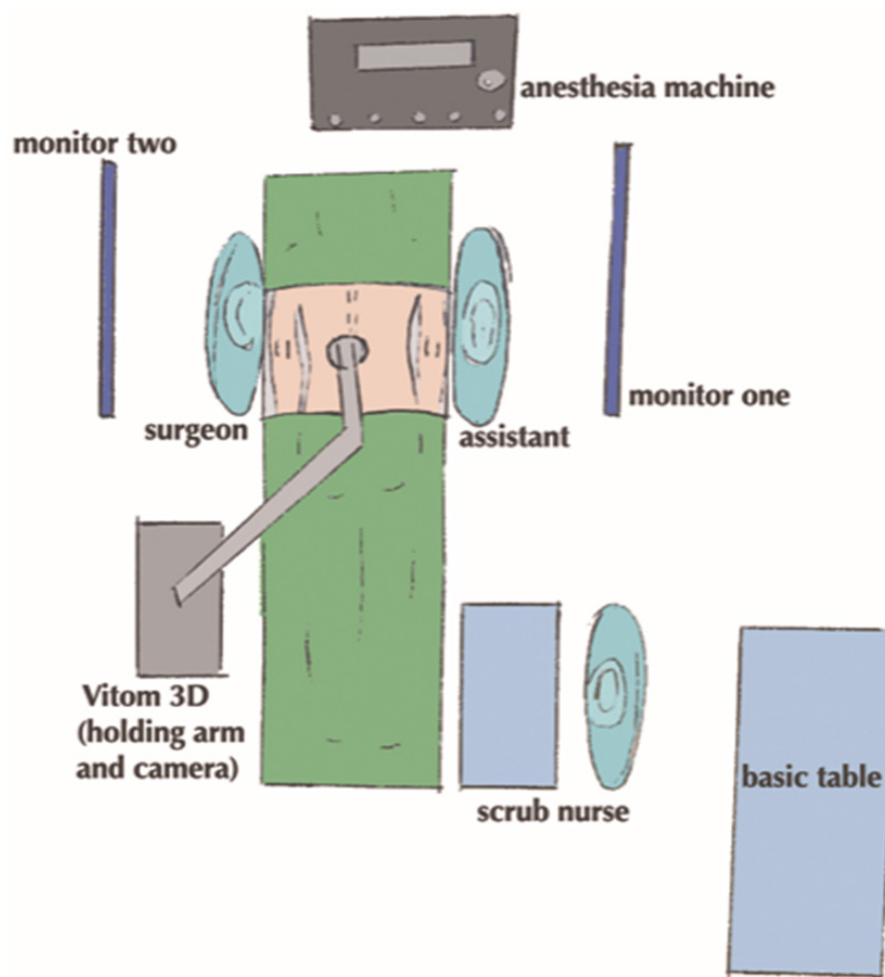


Figure 1. Schematic drawing showing the intra-operative set-up when spinal procedures are performed under Vitom-3D visualization

depth of the operative field compared to the operating microscope, especially with small dimensions of the approach. Once the surgeon feels that the procedure is becoming unsafe due to poor image quality, switching to the operating microscope may be required for better tissue identification and manipulation.

Vitom-3D is one of the exoscopic systems nowadays available for neurosurgical use^[55] [Table 1]. Each of these devices has its strengths and weaknesses, both from the ergonomic and optical point of view. The newer exoscopes can be upgraded combining other technological tools for surgical visualization and planning (navigation, white matter tractography, intra-operative green video angiography). The pros and cons of the different systems must be balanced, and their cost considered when choosing the ideal exoscope within a neurosurgical department.

SPINAL MENINGIOMA SURGERY

Along with the definition of advantages and disadvantages of the exoscope over the operating microscope or endoscope, the increased experience brought to light on the surgical setting in which the use of Vitom-3D could be best indicated. Table 2 summarizes the application of Vitom-3D to spinal procedures, both for degenerative diseases and tumors removal.

Among spinal pathologies, meningioma surgery probably epitomizes the indication for Vitom-3D application. The most frequently reported location for spinal meningiomas is the thoracic spine (67%-84%),

Table 1. Main characteristics of exoscopic system options

Exoscopic system	Optics	Ergonomics	Pros	Cons	Cost
Vitom (Karl Storz, Tuttlingen, Germany)	Focal length: 20-50 mm magnification: 8x to 30x 3D, HD, 4K	The camera is mounted on a fixed pneumatic holder	Extended working distance	Movements are limited by the holder	+
KINEVO (Carl Zeiss AG, Oberkochen, Germany)	Focal length: 200-625 mm magnification: 10x 3D, HD, 4K	A robotic microscope that can be converted into an exoscope	Integrated navigation, ICG, QEVO scope	Heavy, movements require 2 hands, impaired workflow	++++
ORBEYE (Olympus, Tokyo, Japan)	Focal length: 220-550 mm magnification: 26x 3D, HD, 4K	Manual movement utilizing a floor-based arm	Imaging quality	Lack of integrating software	++
Synaptive Modus V (Synaptive Medical, Toronto, Canada)	Focal length: 650 mm magnification: 12.5x 2D, HD	Manual movement utilizing a floor-based arm	Integrated navigation and tractography	Lack of 3D	+++

Table 2. Review of the spinal procedures performed under exoscope visualization

Author	Year	2D/3D	Procedures	Total No. patients	Main findings
Mamelak <i>et al.</i> ^[23]	2010	2D	<ul style="list-style-type: none"> 2 ACDF procedures 2 lumbar microdisectomy 1 lumbar foraminotomy 	5	<ul style="list-style-type: none"> Good image quality More comfortable position Easy to transport Excellent for training and education of residents Less expensive
Shirzadi <i>et al.</i> ^[25]	2012	2D	<ul style="list-style-type: none"> 4 lumbar decompressions (1 level) 7 lumbar decompression (2 levels) 11 lumbar TLIF (1 level) 2 lumbar TLIF (2 levels) 	24	<ul style="list-style-type: none"> Lack of stereopsis Repositioning the holding arm Frequent need for zooming and refocusing
Parihar <i>et al.</i> ^[27]	2016	2D	<ul style="list-style-type: none"> 4 ACDF 2 ACCF 2 lumbar disectomies 1 dorsal meningioma 4 neurofibromas (3 dorsal, 1 cervical) 1 cervical tuberculosis 	14	<ul style="list-style-type: none"> The reduced learning curve of neuroendoscopy
Krishnan <i>et al.</i> ^[35]	2017	2D	<ul style="list-style-type: none"> 3 lumbar decompressions 4 lumbar microdisectomies 2 cervical foraminotomies 1 ACDF procedure 	10	<ul style="list-style-type: none"> Cumbersomeness in repositioning, refocusing, and varying the magnification. Lack of fluorescence filters and navigation tools
Oertel <i>et al.</i> ^[39]	2017	3D	<ul style="list-style-type: none"> 2 ACDF procedures 1 cervical osteosynthesis 1 lumbar decompression 3 lumbar disectomies 1 cervical posterior decompression and fixation 1 TLIF procedure (3 levels) 1 TLIF procedure (1 level) 1 thoracic intraspinal extradural tumor 	11	<ul style="list-style-type: none"> Inferior identification of a bleeding source as compared to the microscope
Khalessi <i>et al.</i> ^[48]	2019	3D	<ul style="list-style-type: none"> 1 ACDF procedure 2 lumbar posterior decompression 	3	<ul style="list-style-type: none"> During the preliminary testing phase, it is advisable to have an operating microscope available in the room
Beez <i>et al.</i> ^[43]	2018	3D	<ul style="list-style-type: none"> myelomeningocele closure 	1	<ul style="list-style-type: none"> The illumination of the OM was considered superior
de Divitiis <i>et al.</i> ^[41]	2019	3D	<ul style="list-style-type: none"> 1 intradural hemangioma 2 dorsal Schwannomas 2 dorsal Meningiomas 	5	<ul style="list-style-type: none"> Excellent image quality. Need for reposition and refocusing when surgical exposure changed from extradural to intradural
Kwan <i>et al.</i> ^[47]	2019	3D	<ul style="list-style-type: none"> 4 ACDF 1 ACCF 3 cervical laminectomies 2 lumbar laminectomies 	10	<ul style="list-style-type: none"> Wear surgical loupes under 3D glasses; interchange between loupes and 3D magnification of the field; use the exoscope as a sterile, high-intensity flexible light source
Barbagallo <i>et al.</i> ^[44]	2019	3D	<ul style="list-style-type: none"> 2 ACDF-procedures 	2	<ul style="list-style-type: none"> Indications to the use of the endoscope: early steps of cervical soft tissue dissection; for cage insertion, which requires free maneuverability of the screw and cage holders under direct vision

ACDF: anterior cervical decompression and fusion; ACCF: anterior cervical corpectomy and fusion; TLIF: transforaminal lumbar interbody fusion

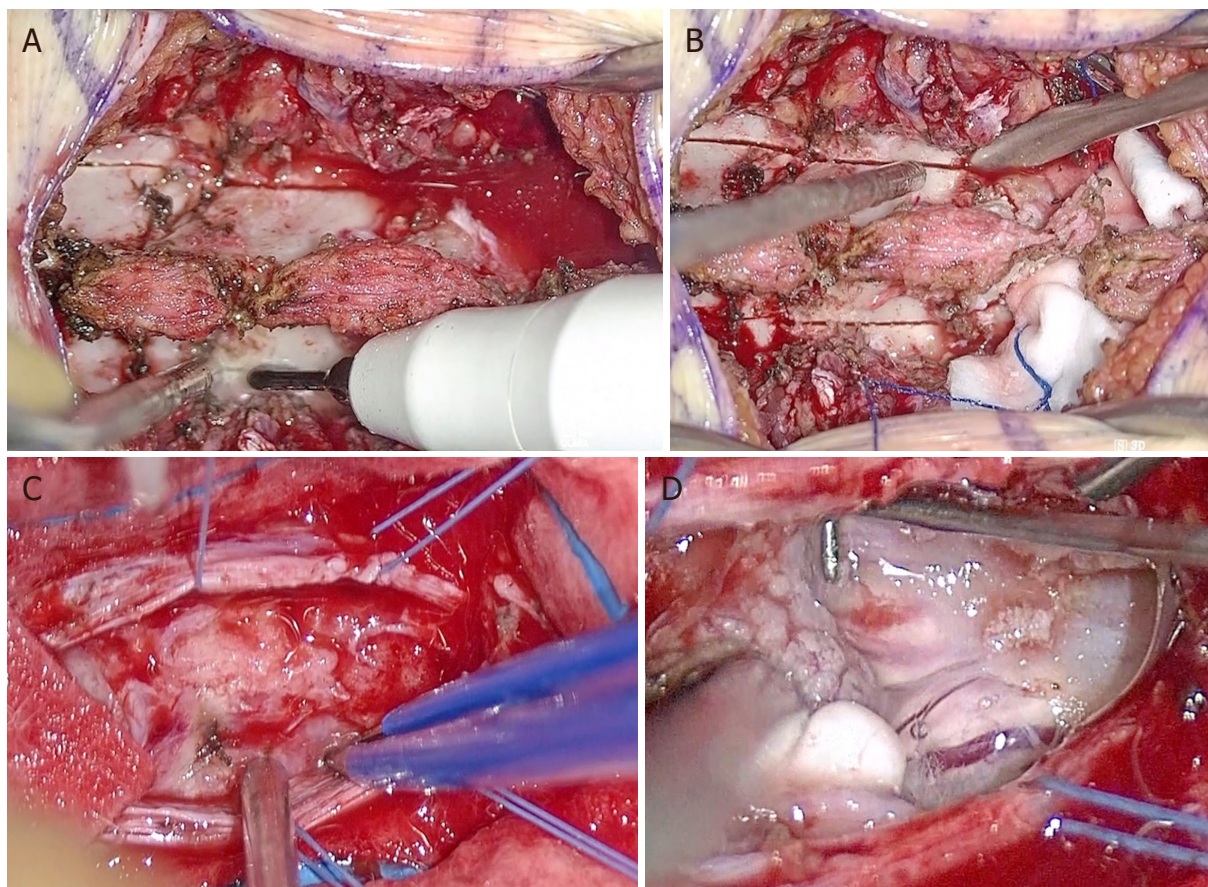


Figure 2. Two levels dorsal laminotomy is performed under visualization of Vitom-3D (A, B); after focus and zoom adjustment, the tumor is exposed and dissected from arachnoidal adhesions (C, D) until total removal is achieved

followed by the cervical spine (14%-27%), and the lumbar spine (2%-14%). At the time of diagnosis, these tumors rarely extend for more than 3 laminae, because of the early occurrence of signs and symptoms of spinal cord compression in their natural history. Considering the above, the optical properties of Vitom-3D, in particular the focal length of 25-60 cm and the large field of view, allow for excellent illumination and magnification of the depth of the surgical field, more in cases of cervical and thoracic meningiomas than lumbar tumors, where the operative field is deeper. Positioning the VITOM camera at the beginning of the surgical approach approximately 35-40 cm above the operative field, all procedures can be performed with the minimal need for repositioning and refocusing at higher magnifications, due to the quite homogeneous depth of exposure [Figure 2].

In this way, ongoing video documentation step-by-step of the surgical procedure with outstanding quality of the images is available for all the surgical room staff and educational purpose. In cases of meningiomas extending for more than three laminae, exoscope adjustments would likely be more often required. During the extradural steps of the procedure, the surgeon, if wished, could operate under direct vision rather than from the VITOM monitor. Still, it is worth to consider the exoscope a teaching tool of great impact and we suggest its utilization during the whole surgery. Besides, the use of the VITOM from skin incision may help in reducing the learning curve that is associated to the introduction on any new surgical instrument. Fluoroscopy is commonly adopted during meningiomas surgery in order to safely tailor the dimension of the approach to tumor extension. The exoscope doesn't need to be transitioned in and out of the operative field during placement of fluoroscopy, which may contribute to increased efficiency. On the counterpart, the need of two monitors for spinal surgery could reduce the working environment ergonomic.

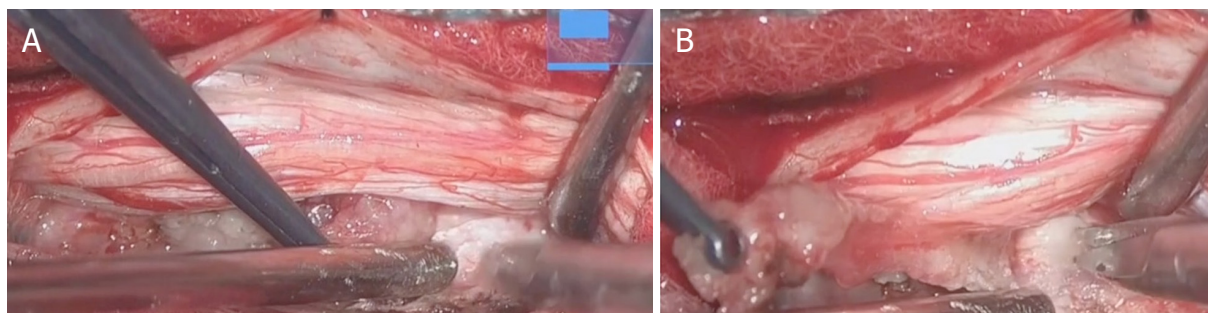


Figure 3. Vitom-3D allows for the identification of spinal meningiomas ventral dural attachment (A); the cleavage plane is followed until complete tumor resection (B)

Oertel *et al.*^[39] reported their experience with only one monitor and the assistance standing right next to the surgeon, both looking at the same screen. However, this is not the usual surgical position and could result in inconvenience. Adjustment of the zoom and focus are required at dural opening, when surgical exposure changes from the extradural to the intradural space; tumor exposure with the identification of cranial and caudal poles and debulking can be usually performed without the need of further modifications. Zoom should be increased for a safer tumor dissection from the arachnoidal plane and for a better identification of the dural attachment, both in cases of ventral and dorsal meningiomas [Figure 3].

Finally, the large working distance eliminates the conflict between surgical instruments and the exoscope and, when required, allows for the placement of traditional spinal instrumentation.

Meningiomas surgery under exoscope visualization is feasible, safe and efficient. VITOM-3D provides excellent visualization of all relevant structures, including spinal cord, surrounding vessels, spinal roots, tumor-nervous parenchyma interface, and dural attachment. The surgical setting with the camera holding arm on the opposite side of the surgeon, the exoscope at the center of the surgical field without conflicting with his/her dominant hand, and the monitor just in front of the surgeon operating at the side of the patient, allows for maximal comfort of the surgeon that stands upright with arms in a bent and relaxed position during all the surgical steps, and operates from the video monitor. It stands clear that the use of Vitom-3D for meningiomas removal greatly depends on tumor size, consistency, relationship to surrounding neurovascular structures, and surgeon's experience. Switching to the operating microscope, if deemed safer, should always be taken into account.

ILLUSTRATIVE CASE

A seventeen-year-old young lady came to our attention because of the acute onset of spinal cord compression syndrome. The neurological examination revealed walking impairment, lower limbs strength deficit, hyperelicitable Achilles and patellar reflexes, positive Romberg sign, urinary incontinence and left hearing loss. Magnetic resonance of the brain and spine showed images suggestive for left acoustic neurinoma, left cavernous sinus meningioma, intradural intramedullary tumor mass at the cranio-cervical junction, and a dorsal intradural-extramedullary meningioma. She underwent genetic screening and neurofibromatosis type 2 was diagnosed. Firstly, the patient underwent surgery for the removal of the medullo-cervical tumor with the assistance of intraoperative neuromonitoring. The surgical procedure was uneventful and the histological diagnosis revealed a low-grade astrocytoma. After complete recovery, the patient was scheduled for the surgical removal of the dorsal tumor. Intraoperative neuromonitoring was used. A skin-to-skin approach under Vitom-3D visualization was performed [Video 1]. Surgery was performed following the common steps of spinal procedures. After a two-level D2-D3 laminoplasty, dura was opened and tumor mass was exposed. Macroscopic appearance was consistent with a spinal

meningioma. The rostral and caudal poles were identified; the tumor was debulked and dissected from the arachnoidal adherences. The dorsal dural attachment was visualized and the tumor was released. En bloc gross total resection was achieved with no intra-operative complications. The exoscope visualization provided excellent images quality, both during the extradural and intradural surgical steps. After initial positioning of the camera 30 cm above the surgical field, repositioning was never required. Zooming and focusing were adjusted after dural opening; zoom was further increased during tumor dissection. Histological diagnosis confirmed a WHO I spinal meningioma. Clinical and radiological follow-up at three months demonstrated total removal of the meningiomas and walking improvement. Further treatment for the other lesions is planned.

CONCLUSION

Vitom-3D has recently entered the field of neurosurgery and, in selected case, it represents an alternative visualization tool to the operating microscope. Working environment ergonomics and trainees learning experience are the most relevant benefits associated with the use of exoscope. The optical properties make it best suited for spinal procedures rather than intracranial surgery, both for degenerative diseases and tumors removal. In particular, spinal meningiomas removal under skin-to-skin Vitom-3D visualization only seems feasible, efficient, and safe. Indications to the use of Vitom-3D greatly depend on tumor size, consistency, relationship to surrounding neurovascular structures, and surgeon's experience. Switching to the operating microscope, if deemed safer, should always be considered. Further studies, including larger homogenous series, are needed to better define advantages and limitations of the exoscope in meningiomas surgery as compared to the operating microscope.

DECLARATIONS

Authors' contributions

Made substantial contribution to conception of the study: de Divitiis O, Denaro L

Prepared the manuscript draft: d'Avella E, Baro V

Responsible for images and supplementary material: Sacco M, Somma T

Critically revised the final version of the manuscript: de Divitiis O, Turgut M

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not Applicable.

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Review

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Predictors for procedural success and all-cause mortality in patients undergoing transcatheter mitral valve edge-to-edge repair for mitral regurgitation

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Abstract

A growing body of evidence shows that transcatheter mitral valve edge-to-edge repair (TMVr) for mitral regurgitation (MR) improves symptoms and prognosis of patients with heart failure. Still, as recently shown by two large randomized controlled trials (COAPT and MITRA-FR), there is differing information on which patients have the largest benefit. We aimed to summarize the current knowledge of clinical and anatomic predictors for acute procedural failure and long-term all-cause mortality after TMVr. TMVr is an effective treatment option for patients with symptomatic MR fulfilling certain echocardiographic and clinical criteria or being ineligible for surgery despite optimal medical therapy. Acute procedural failure is influenced by anatomic features of the mitral valve, among those are increased tenting and mitral valve leaflet configuration, leaflet-to-annulus index, as well as the mitral valve opening area. In contrast, anatomy of the mitral valve plays a minor role in predicting all-cause mortality after TMVr. This endpoint is associated with patient comorbidities (e.g., renal failure and chronic lung disease), severe heart failure as expressed by New York Heart Association functional class (NYHA) IV, left and right heart dysfunction, laboratory parameters (NT-proBNP), clinical scoring systems (STS and EuroScore), and procedural MR reduction. In patients undergoing TMVr for severe MR, careful preprocedural evaluation of relevant



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comorbidities, mitral valve anatomy, as well as left and right heart function can provide detailed prognostic value regarding acute procedural success and long-term survival.

Keywords: MitraClip, transcatheter mitral valve edge-to-edge repair, predictors for mortality, secondary mitral regurgitation, primary mitral regurgitation, heart failure, percutaneous mitral valve repair

INTRODUCTION

Mitral regurgitation (MR) is a major contributor to cardiovascular morbidity and mortality in patients with heart failure^[1-3]. With more than ten years of clinical experience and continuous technical development, transcatheter mitral valve edge-to-edge repair (TMVr) is a well-established treatment option for patients suffering from primary (PMR) or secondary (SMR) mitral regurgitation. In PMR patients, structural damage of different parts of the valvular apparatus itself can lead to development of MR, while SMR is caused by atrial and ventricular pathologies^[4]. Accordingly, PMR and SMR themselves form heterogeneous groups and can occur in combination, a fact which must be taken into account for therapeutic decisions and device selection^[5]. In PMR, TMVr is recommended in case of prohibitive surgical risk and absence of adverse anatomic features, based on the results of the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trials^[6-8]. For SMR, the 2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation does not include surgical ineligibility as a primary criterium for TMVr usage. TMVr can be the therapy of choice for severe SMR with left ventricular ejection fraction (LV-EF) between 20% to 50%, left ventricular end diastolic diameter (LV-EDD) < 7.0 cm, and persistence of clinical signs and symptoms of heart failure despite of optimal guideline-recommended medical treatment (GDMT) and, if applicable, cardiac resynchronization therapy^[8-11]. These recommendations are based on two large randomized-controlled trials (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation - COAPT and Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation - MITRA-FR), which revealed different findings regarding the prognostic benefit of TMVr treatment on top of GDMT in SMR patients^[12,13]. Recently, several theories have been proposed to deliver potential explanations for these varying results^[14-19]. Undoubtedly, patient selection for TMVr could be a crucial factor influencing not only clinical outcome but also procedural success. The influence of cardiac anatomic parameters on outcome after TMVr is less understood, but has gained recent attention to optimize procedural and clinical results^[20]. In this review, we evaluate the current data on the impact of anatomical and functional left and right heart features, as well as clinical parameters and comorbidities on acute procedural success/failure and mortality after TMVr.

ENDPOINTS AND PATIENT COHORT

The two common endpoints in outcome analysis after TMVr that this article focuses on are acute procedural failure (APF) and all-cause and/or cardiac mortality^[21-24]. The Mitral Valve Academic Research Consortium (MVARC) differentiates between technical, device, procedural, and patient success^[24]. In other words, APF is the absence of procedural success, which consists of technical success at exit from the catheterization laboratory, absence of procedural mortality or stroke, and reduction to MR 2+ or lower^[24]. Clearly, reasons for APF could be inability of device implantation due to individual anatomical features or generation of significant mitral valve stenosis represented by increasing mean mitral valve pressure gradients (MV mean PG). MVARC recommends postprocedural MV mean PG not to exceed 5 mmHg^[24]. Secondly, APF can be caused by insufficient MR reduction despite successful implantation of the device. According to MVARC criteria, procedural results are defined as optimal in case of absent or trace postprocedural MR^[24].

PMR and SMR are two pathophysiologically different entities of mitral valve disease which both lead to similar clinical signs and symptoms. We believe that based on vast differences in baseline clinical characteristics, cardiac anatomy and function, baseline procedural risk before TMVr, and outcome after TMVr, patients with SMR and PMR should be analyzed separately^[25]. This viewpoint is supported by an increasing body of evidence. Nevertheless, the majority of registries have reported on cohorts of both PMR and SMR without dedicated analysis of separate entities. Therefore, this review divides each section by MR sub-collectives (composed PMR and SMR, PMR only, and SMR only collectives).

PREDICTING PROCEDURAL SUCCESS AND FAILURE IN PATIENTS UNDERGOING TMVR FOR MR

Comprehensive, unambiguous analysis of procedural success and failure is hindered by varying definitions in studies on TMVr. Albeit effective MR reduction is feasible in both PMR and SMR, some TMVr studies suggest more profound MR reduction in patients with PMR^[26], while some report higher rates of APF in PMR^[27] and some did not find any differences^[28]. Comparisons between procedural MR reduction in patients with PMR and patients with SMR are further complicated by different definitions of MR severity and challenging assessment of quantitative MR parameters after device placement.

Composed PMR and SMR patient collective

Dörr *et al.*^[29] identified BNP levels and two biomarkers of cardiac fibrotic alterations, galectin-3 (Gal-3) and suppression of tumorigenicity 2 (ST2), as predictors for successful MR reduction by ≥ 2 grades. It can be assumed that patients with higher levels of Gal-3 and ST2 are in a more advanced state of heart failure with ongoing fibrotic damage. This may alter the cardiac response to TMVr treatment, hinder reverse remodeling, and result in worse procedural outcomes.

Furthermore, Thaden *et al.*^[30] sought to determine predictors of hemodynamic success, which was defined as at least 40% reduction of left atrial V wave compared to baseline. Multivariable analysis revealed flail scallop [Figure 1A], single jet or multiple jets originating from a single scallop [Figure 1B], and good or excellent three-dimensional image quality as independent predictors for hemodynamic success. Besides that, preprocedural MV mean PG, mitral annular calcification, and deployment of more than one clip predicted development of mitral stenosis with a mean gradient greater than 5 mmHg.

PMR only collective

Detailed three-dimensional (3D) analysis of the MV can help to identify predictors for optimal MR reduction after TMVr. In PMR, low MV leaflet tenting volume [Figure 1C] and height [Figure 1D] were predictive of optimal MR reduction^[31]. Even in the case of Carpentier classification type II PMR with prolapse of leaflet, concomitant regional tenting patterns may complicate optimal MR reduction^[31]. Another 3D analysis found a novel predictive parameter called MV leaflet-to-annulus index (LAI), defined as the ratio of the sum of the anterior and posterior MV leaflet and the anteroposterior mitral annular length [Figure 1E]. Low LAI indicates a leaflet-to-annulus disproportionality and significantly predicts residual MR after TMVr^[32]. Identifying patients with inadequate MR reduction is important as relevant residual MR is associated with worse survival rates in several studies^[33-37].

Besides these predictors for residual MR, development of postprocedural mitral stenosis can lead to APF. Two predictors of a MV mean PG ≤ 4 mmHg after clip deployment in PMR were preprocedural mitral valve opening area of (MVOA) ≥ 3.94 cm² and medial-lateral diameter of left ventricle (LV) inflow orifice ≥ 3.23 cm for patients receiving one implanted clip. In case of two clips, cut-offs were 4.82 cm² and 3.29 cm, respectively^[38].

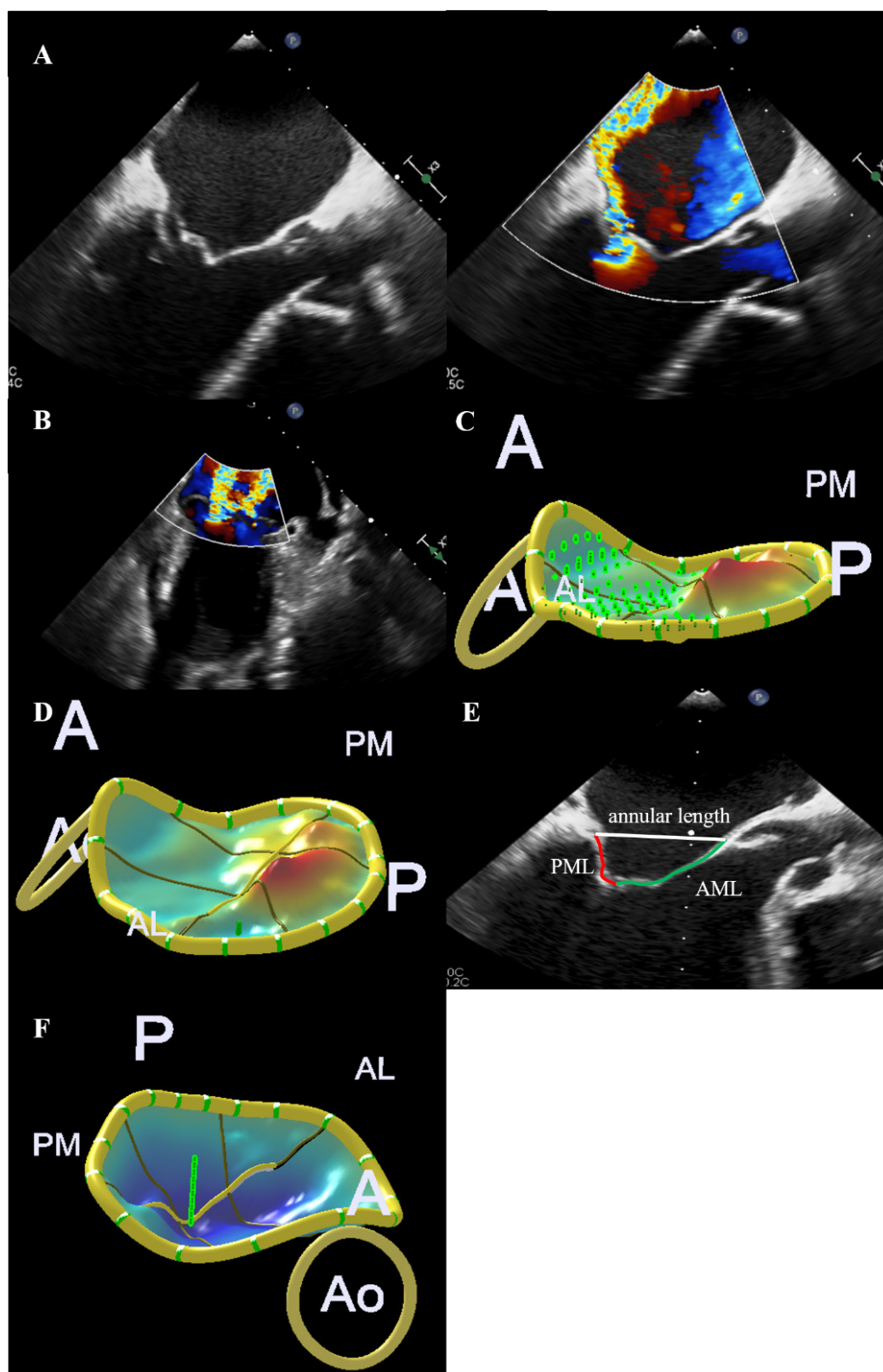


Figure 1. Anatomic predictors for procedural success and failure after TMVr. A: flail scallop is associated with worse hemodynamic success after TMVr in primary mitral regurgitation patients; B: A single or multiple jets originating from one flail scallop are associated with hemodynamic success after TMVr; lower tenting volume (C) and tenting height (D) are associated with optimal MR reduction; E: low mitral valve leaflet-to-annulus index predicts residual MR; F: increasing annular height predicts optimal MR reduction. A: anterior; P: posterior; AL: anterolateral; PM: posteromedial; Ao: aortic valve; PML: posterior mitral valve leaflet; AML: anterior mitral valve leaflet; TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation

Table 1. Left heart: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
LV-EF	≤ 25%	SMR	[48]
	< 27%	SMR	[46]
	< 30%	SMR	[43]
	< 30%	SMR/PMR	[35,42,57,76]
	*	SMR/PMR	[25,28]
Stroke volume	*	PMR	[45]
LV dysfunction with and without CAD	**	PMR	[45]
LV-EDV	> 216 mL	SMR	[48]
LV-EDD	*	SMR	[49]
	*	SMR/PMR***	[44]
Afib	**	SMR	[47,48]
	**	SMR/PMR	[51]
LA-EF change	*	SMR/PMR	[53]
LA diameter	≥ 55 mm	SMR/PMR	[52]

*Continuous parameter; **binary parameter; ***cardiac death. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; LV-EF: left ventricular ejection fraction; CAD: coronary artery disease; LV-EDV: left ventricular end diastolic volume; LV-EDD: left ventricular end diastolic diameter; Afib: atrial fibrillation; LA-EF: left ventricular ejection fraction; LA: left atrium

SMR only collective

For SMR, anatomic parameters of the mitral valve that could influence procedural success are mainly determined by atrio-ventricular architecture since leaflets do not have structural damage by definition. Several anatomic configurations of the MV are associated with optimal MR reduction by TMVr: Among those are increasing annular height [Figure 1F]^[31], less planar MV anatomy^[31,39-41] and, alike in PMR, the LAI parameter^[32]. Stolfo *et al.*^[41] identified left ventricular end diastolic volume index and anteroposterior mitral annulus diameter as independent predictors for device failure according to MVARC criteria^[24,41]. More severe dilation of the left ventricle leads to flattening deformation of the MV apparatus complicating TMVr procedure, while larger mitral annulus diameters impair proper leaflet coaptation.

Comparable to PMR, preprocedural MVOA and medial-lateral diameter of LV inflow orifice can also predict postprocedural mitral stenosis. For one and two clips, the cut-off values were 3.77 cm²/5.05 cm² and 3.03 cm/3.39 cm, respectively^[38].

PREDICTING ALL-CAUSE MORTALITY IN PATIENTS UNDERGOING TMVR FOR MR

Within the last ten years, several reports aimed at identifying predictors for all-cause mortality in patients with MR after TMVr. Most of these studies were based on a composed collective of patients with PMR and SMR, while large, dedicated data sets for SMR and especially PMR alone are rare.

LEFT VENTRICULAR FUNCTION AND DIMENSIONS

Composed PMR and SMR patient collective

One of the main predictors for all-cause mortality in patients with MR undergoing TMVr is impairment of left ventricular function, represented by reduced LV-EF. Several analyses identified impaired LV-EF as highly predictive for five-year^[28,35] and long-term mortality^[25,42,43] [Table 1]. Surprisingly, left ventricular size and geometry do not seem to play a major role in predicting TMVr all-cause mortality when including both SMR and PMR patients into multivariable models. Only one study specifically focusing on cardiac mortality reported increased LV-EDD as a significant predictor^[44] [Table 1].

PMR only collective

In patients with PMR, impaired left ventricular stroke volume and LV-EF are predictors for all-cause mortality [Table 1]^[45].

SMR only collective

Consistently, impaired LV-EF leads to significantly worsened long-term survival in patients with SMR after TMVr^[25,46-48]. In contrast to mixed cohort analysis, severe LV dilatation, measured either by LV-EDD^[49] or left ventricular end diastolic volume^[48], was identified as a predictor for all-cause mortality in patients with SMR [Table 1]. After publication of the COAPT and MITRA-FR trials, a discussion about possible reasons for the diverging prognostic results has evolved and several explanations have been proposed. Among them are operator experience, intensity of concomitant medical therapy, progression of heart failure at baseline, and procedural MR reduction. Since mean left ventricular end diastolic volume was very high in MITRA-FR, patients in this trial might have had end-stage heart failure with severe LV dilatation. The proportionality of MR severity to LV dilatation, quantified by ratio of effective regurgitant orifice area to LV end diastolic volume, has recently gained attention^[14,50]. Latest analyses showed that the proportionality concept as a prognostic framework might be applicable to medically treated SMR patients. Its influence on prognosis in TMVr-treated patients is probably less important, as TMVr effectively reduces MR and thus abolishes one component of the proportionality equation^[17,19].

LEFT ATRIAL FUNCTION AND DIMENSIONS

Composed PMR and SMR patient collective

Atrial fibrillation or absence of sinus rhythm, as indicators of impaired LA function in addition to LA dilation, are linked to worse TMVr survival^[42,51,52]. Severe LA dilatation with a diameter ≥ 55 mm seems to be a highly predictive cut-off value^[52]. In contrast, improvement of LA ejection fraction from baseline to short term follow up (three to six month) is associated with lower all-cause long-term mortality^[53] [Table 1].

SMR only collective

While dedicated data for PMR patients are missing, atrial fibrillation^[47,48] and increased LA volume^[47] are associated with impaired long-term survival in SMR patients [Table 1]. Left atrial dysfunction in SMR patients recently gained attention as this condition can lead to MR in absence of severe systolic LV dysfunction. This pathology called atrial secondary mitral regurgitation (ASMR) is caused by either atrial fibrillation or heart failure with preserved ejection fraction (HFpEF), as both increase LA pressure and volume leading to annular flattening and alteration of left ventricular atrioventricular hemodynamics^[54]. As HFpEF patients with SMR were excluded from large controlled randomized trials (COAPT or MITRA-FR)^[12,13], but undergo TMVr procedure in real-world clinical practice, impact of ASMR on survival and procedural success warrants further investigation.

MITRAL VALVE ANATOMY, HEMODYNAMICS, AND PROCEDURAL SUCCESS

Composed PMR and SMR patient collective

Elevated MV mean PG was identified as highly predictive in terms of all-cause mortality, both for preprocedural and postprocedural measurements. TMVr increases MV mean PG by reduction of mitral valve opening area^[27,36,55] [Table 2]. Additionally, previous MV surgery has been reported to have negative influence on long-term outcome^[56]. Success of TMVr procedure itself is crucial for reduction of long-term mortality and reflects the benefit of this interventional approach on MR treatment. Absence of procedural MR reduction and residual MR after procedure lead to severely impaired long-term survival^[25,35,36,56-60] [Table 2].

PMR only collective

In PMR patients, postprocedural MV mean PG is a significant predictor for survival^[61] [Table 2].

SMR only collective

Similar to findings in the composed SMR/PMR collective, residual SMR is a major factor contributing to mortality following TMVr procedure^[33,49]. In particular, postprocedural MR vena contracta area is

Table 2. Mitral valve: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
MV mean PG (pre)	> 1.5 mmHg	SMR/PMR	[27]
	*	SMR/PMR	[34,36]
MV mean PG (post)	> 5 mmHg (invasive)	SMR/PMR	[55]
	> 4.4 mmHg (echo)	SMR/PMR	[55]
Acute procedural failure	****	SMR/PMR	[57,76,87]
Residual MR	≥ 2+	SMR	[33]
	≥ 2+	SMR***	[49]
	≥ 3+	SMR	[33]
	≥ 2+	SMR/PMR	[32,58]
	≥ 3+	SMR/PMR	[59]
	*	SMR/PMR	[25,34,36,56]
	*	SMR/PMR***	[44]
MR recurrence < 2 years	≥ 2+	SMR/PMR	[35]
VCA (post)	> 25 mm ²	SMR	[62]
Previous MV surgery	**	SMR/PMR	[56]

*Continuous parameter; **binary parameter; ***cardiac death; ****operator-reported failure, conversion to surgery, abortion of procedure or severe residual mitral regurgitation. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; PG: pressure gradient; VCA: vena contracta area; MV: mitral valve

associated with worse long-term outcome^[62]. Mitral valve anatomy itself seems to play a minor role in predicting long-term mortality after TMVr [Table 2]. The only MV configuration that impairs outcome in terms of higher MR severity at follow-up examination seems to be restricted posterior mitral valve leaflet motion defined as posterior mitral valve leaflet tethering angle > 45°^[63]. Whether posterior mitral valve leaflet tethering impacts not only procedural success but also long-term mortality has not been shown so far.

The prognostic role of ischemic origin of SMR has been studied by several groups. Apparently, predictors for all-cause mortality could be different in ischemic versus non-ischemic SMR^[64]. Tricuspid annular plane excursion, renal failure, diabetes mellitus, previous heart surgery, and coronary artery bypass graft are predictive for all-cause mortality in ischemic, but not in non-ischemic SMR^[64]. Besides ischemic and non-ischemic subgroups, SMR etiologies can be separated by LV-LA function. Among those is ASMR, as previously mentioned^[54,65,66]. While our knowledge of anatomy and pathophysiology of ASMR is growing, specific predictors for all-cause mortality after TMVr are so far lacking^[66].

RIGHT VENTRICULAR FUNCTION AND PULMONARY HYPERTENSION

Composed PMR and SMR patient collective

Data on right ventricular (RV) dysfunction in composed PMR/SMR collectives are absent. Nevertheless, pulmonary hypertension has been shown to impair prognosis as it is associated with worse long-term survival^[27,67-69]. Cut-off values for systolic pulmonary artery pressure as a measurement of pulmonary hypertension vary between 37 mmHg and 60 mmHg^[67] [Table 3].

SMR only collective

In contrast to the lack of data for PMR patients, there is a growing body of knowledge that RV dysfunction and pulmonary hypertension in SMR patients are crucial factors for the prognosis after TMVr, pulmonary hypertension (as expressed by elevated systolic pulmonary artery pressure) is also associated with long-term mortality in SMR patients [Table 3]^[49]. Obviously, pulmonary hypertension due to left ventricular and atrial dysfunction and RV function are closely linked. Presence of RV dysfunction, as expressed by impaired tricuspid annular plane excursion or RV peak systolic velocity, leads to biventricular failure [Table 3]^[47,70-72]. Importantly, TMVr treatment is capable of improving RV function. One study found an improvement of tricuspid annular plane excursion by 4 mm and peak systolic velocity by 4 cm/s at 6 months follow up^[73].

Table 3. Pulmonary system and right heart: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
CLD	**	SMR/PMR	[83]
sPAP	> 50 mmHg	SMR	[88]
	*	SMR***	[49]
	*	SMR/PMR	[87]
	> 45 mmHg	SMR/PMR	[27]
	> 50 mmHg	SMR/PMR	[67]
	37-50 mmHg	SMR/PMR	[67]
	> 60 mmHg	SMR/PMR	[37]
RVSP	*	SMR	[78]
PSV (DTI)	< 9.5 cm/s	SMR	[72]
TAPSE	< 15 mm	SMR	[71]
	≤ 16 mm	SMR	[70]
	*	SMR (ischemic)	[64]

*Continuous parameter; **binary parameter; ***cardiac death. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; CLD: chronic lung disease; sPAP: systolic pulmonary artery pressure; PSV: peak systolic velocity; DTI: doppler tissue imaging; TAPSE: tricuspid annular plane systolic; RVSP: right ventricular systolic pressure

Table 4. Tricuspid and aortic valve: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
TR (pre)	*	SMR	[77]
	≥ 3+	SMR/PMR	[37,56,57,74,76,87]
TR (post)	*	SMR	[43]
Previous AoV intervention	**	SMR/PMR	[42,57,76,87]
Moderate AR	**	SMR/PMR	[75]

*Ordinal parameter; **binary parameter. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; TR: tricuspid regurgitation; AoV: aortic valve; AR: aortic regurgitation

CONCOMITANT TRICUSPID AND AORTIC VALVE DISEASE

Composed PMR and SMR patient collective

The relevance of concomitant valve disease in patients treated with TMVr has been shown for tricuspid and aortic valve regurgitation. Severity of pre- and postprocedural moderate or severe tricuspid regurgitation (TR) has repeatedly been shown as an important factor worsening long-term mortality [Table 4]^[37,42,43,56,74]. Whether TR contributes alone to dismal outcome or only in conjunction with RV dysfunction is controversial and has to be further assessed. In addition, a recent study reported about the negative impact of moderate aortic regurgitation on survival [Table 4]^[75]. Prior intervention of the aortic valve has repeatedly been reported as a negative prognostic factor for patients treated with TMVr^[42,57,76].

SMR only collective

Data about the role of concomitant TR in SMR patients are ambiguous, while again dedicated data of concomitant valvular pathology for PMR patients undergoing TMVr is unknown. While some authors found preprocedural severe TR as a predictor worsening prognosis after TMVr^[77] others, including the large COAPT trial with echocardiographic core lab assessment, did not^[25,78] [Table 4]. We believe that moderate or severe TR in patients with SMR is tightly connected to the prevalent biventricular failure, thus a bystander. Whether isolated TR in the absence of RV dysfunction might yield prognostic value in TMVr-SMR patients has yet to be shown.

RENAL FUNCTION

Undoubtedly shown by a multitude of studies, impaired kidney function (defined as either reduced estimated glomerular filtration rate, elevated levels of creatinine or need of dialysis) is one of the strongest predictors for all-cause mortality in TMVr-treated patients^[25,27,28,32,33,42,43,53,79,80]. Those findings are consistent in PMR,

Table 5. Renal function: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
GFR	< 30 mL/min	SMR	[72]
	30-60 mL/min	SMR	[43]
	< 50 mL/min	SMR	[62]
	*	SMR	[53]
	*	SMR/PMR	[25,79]
	< 60 mL/min	SMR/PMR***	[44]
	< 60 mL/min	SMR/PMR	[37,58]
Creatinine	> 1.5 mg/dL	SMR/PMR	[35,42,57,76,87]
	> 2 mg/dL	SMR/PMR	[27]
	*	SMR/PMR	[83]
	**	PMR	[45]
Cystatin C	1.7 mg/dL vs. 2.4 mg/dL****	SMR/PMR	[89]
NGAL	132.0 ng/mL vs. 242.0 ng/mL****	SMR/PMR	[89]

*Continuous parameter; **binary parameter; ***cardiac death; ****survivors vs. non survivors. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; GFR: glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin

Table 6. Parameters of heart failure: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
NYHA	*	SMR	[77]
	≥ III	SMR	[86]
	*	SMR/PMR***	[80]
	IV	SMR/PMR***	[44]
	IV	SMR/PMR	[37,57,58,60,76,85,87,90]
NT-proBNP	≥ 10000 pg/mL	SMR	[48]
	Per 10 ³ increase	SMR (non-ischemic)	[64]
	Log	SMR/PMR***	[80]
	Log	SMR/PMR	[85]
	≥ 5000 µg/L	SMR/PMR	[56]
Prior cardiac decompensation	**	SMR/PMR	[35,42]
Prior cardiac hospitalization	**	SMR	[86]
Length of hospitalization	> 2 days	SMR	[86]

*Ordinal parameter; **binary parameter; ***cardiac death. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; NYHA: New York Heart Association

SMR and composed PMR/SMR collectives. Reported cut-off values in terms of all-cause mortality range from < 60 mL/min to < 30 mL/min for GRF and 1.5 mg/dL to 2.0 mg/dL for creatinine levels [Table 5]. In a composed SMR/PMR collective, other laboratory parameters of kidney function including Cystatin C and neutrophil gelatinase-associated lipocalin were also associated with worse outcome after TMVr^[81,82] [Table 5].

COMORBIDITIES AND HEART FAILURE-RELATED PARAMETERS

Besides kidney function, a broad variety of clinical conditions and comorbidities are accompanied by worse survival rates. Among those are chronic lung disease^[42,83], heart failure as expressed by elevated levels of the natriuretic peptide NTpro-BNP^[80,84] or worse New York Heart Association functional class (NYHA) functional class^[42,57,58,60,80] [Table 6], anemia^[28,85], elevated mean arterial blood pressure^[85], impaired exercise capacity (six minute walk test)^[74], and peripheral artery disease^[42] [Table 7]. Integrating several of the aforementioned conditions and comorbidities, the Society of Thoracic Surgery (STS) score as well as the EuroScore (logistic and EuroScore II) have been shown to predict outcome after TMVr^[35]. Reported cut-offs are ≥ 20 for logistic EuroScore and ≥ 12 for STS Score [Table 7]. As advanced age comes along with a higher burden of comorbidities^[28,62,64,80,83,86] and male patients entail a higher number of cardiac risk factors, these demographics diminish prognosis^[53,78] [Table 7].

DOES THE “IDEAL” TMVR PATIENT EXIST?

Taking into account the broad variety of cardiac and extracardiac conditions influencing outcome after TMVr, it seems difficult to identify the “ideal” patient for this procedure. Generally speaking, survival

Table 7. Comorbidities, demographics and risk scores: predictors for all-cause mortality after TMVr for MR

Parameter	Cut-off	MR etiology	Ref.
PAD	**	SMR	[77]
	**	SMR/PMR	[57,76,87]
Anemia	**	SMR/PMR	[28,57,76]
Hb	*	SMR/PMR	[85]
Blood transfusion	≥ 2 Units	SMR	[86]
MAP	*	SMR/PMR	[85]
Ischemic MR	**	SMR/PMR	[60]
Peak VO ₂	*	SMR	[47]
Age	*	SMR (non-ischemic)	[64]
	> 70 years	SMR	[86]
	*	SMR/PMR	[62,83]
	**	SMR/PMR***	[28,80]
Sex	**	SMR	[78]
	**	SMR/PMR	[53]
Log ES	*	SMR (ischemic)	[64]
	*	SMR	[45]
	*	SMR/PMR***	[80]
	> 20	SMR/PMR***	[80]
	≥ 20	SMR/PMR	[36]
STS	*	SMR	[78]
	*	SMR/PMR***	[80]
	≥ 12	SMR/PMR***	[80]
	≥ 12	SMR/PMR	[58]

*Continuous parameter; **binary parameter. TMVr: transcatheter mitral valve edge-to-edge repair; MR: mitral regurgitation; SMR: secondary mitral regurgitation; PMR: primary mitral regurgitation; PAD: peripheral artery disease; Hb: hemoglobin; MAP: mean arterial pressure; Peak VO₂: maximum oxygen uptake; log ES: logistic euroscore; STS: society of thoracic surgery risk score

prognosis correlates with the patient's overall health status, non-cardiac comorbidities, and most importantly, degree and characteristics of heart failure. This is intricate, as profound surgical risk and comorbidities often are the main reason for considering TMVr as primary therapy.

First and foremost, successful MR reduction by device implantation is the key for any clinical or prognostic improvement. Guided by proper two- and three-dimensional echocardiography, an experienced interventionalist is capable of achieving maximum procedural reduction of MR without generation of MV stenosis. Ideal prerequisites would be a low mean mitral valve pressure gradient, large mitral valve opening area, and wide LV inflow diameter. Furthermore, MV geometry, as influenced by left ventricular and atrial anatomy, should be preserved, without flattening of the MV annulus, lowering of the anterior mitral valve angle, or disproportionate leaflet-to annulus ratio. Furthermore, if there is a concomitant secondary component to PMR, tenting volume and height should be low.

In terms of survival, the ideal patient is believed to present with a minimal spectrum of extracardiac comorbidities, no concomitant aortic, tricuspid, or pulmonic valve pathologies, moderately impaired LV function, and absence of right ventricular failure and pulmonary hypertension. Generally speaking, after successful intervention, the patients' overall health status determines survival prognosis, while anatomic features seem to play a minor role for further prognosis.

CONCLUSION

With successful MR reduction rates of more than 95% in the majority of studies, the TMVr procedure for severe MR can be performed effectively and safely in a wide variety of mitral valve configurations with different underlying left heart diseases. For acute procedural failure, anatomic and hemodynamic parameters of the MV are important predictors. In contrast, clinical baseline characteristics, comorbidities, atrioventricular echocardiographic parameters, and procedural MR reduction are important for long-term prognosis.

Since patients with PMR have severe structural pathologies of the MV, leaflet configuration seems to be more important compared to SMR patients. Therefore, we recommend stricter separation of SMR and PMR etiology within studies, as well as differentiating “sub-etologies” of SMR (ischemic MR, non-ischemic MR, ASMR, and HFmrEF-SMR), which could be done by multi-center pooling of data. A prerequisite is comprehensive guideline-recommended echocardiographic assessments of cardiac anatomy and function, also including the right heart and pulmonary vasculature. This integrated approach is challenging but would facilitate further understanding of pathophysiology and outcome in a diversity of SMR subtypes undergoing TMVr, thereby improving patient selection and procedural MR reduction to achieve optimal outcome after TMVr.

DECLARATIONS

Authors' contributions

Drafting of conceptual and methodologic framework: Stolz L, Orban M, Hausleiter J, Orban M

Manuscript writing: Stolz L, Orban M, Orban M

Manuscript review: Braun D, Nabauer M, Hagl C, Massberg S, Hausleiter J

Availability of data and materials

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Conflicts of interest

Martin Orban has received speaker honoraria from SedanaMedical, AstraZeneca and Bayer Vital. Michael Nabauer, Mathias Orban and Daniel Braun have received speaker honoraria from Abbott Vascular. Jörg Hausleiter has received speaker honoraria from Abbott Vascular and Edwards Lifesciences. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Robotic surgery of gallbladder cancer

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Abstract

Aim: The aim of this study was to describe our technique for the surgical treatment of clinically suspected or incidentally diagnosed gallbladder cancer (GBC) and to report the outcomes of our experience.

Methods: This is a retrospective observational study including consecutive patients operated by a robotic approach for the surgical treatment of clinically suspected or incidentally diagnosed GBC (with the intent of radical resection after index cholecystectomy) performed between January 2017 and December 2019. Clinical outcomes and technical details related to the robotic approach were analyzed.

Results: During the study period, 8 patients underwent robotic radical cholecystectomy with lymphadenectomy and atypical resection of segments IVb-V. No conversion or major complications occurred intraoperatively. All patients underwent a radical resection. There were one Clavien-Dindo grade II and one grade IIIb complication. Median hospital stay was 6 days (range 5-11). At a median follow-up of 17.5 months (range 2.3-73), all patients are alive and free from disease except one who had peritoneal recurrence and underwent chemotherapy. No trocar site recurrence was observed.

Conclusion: The present study describes a standardized step-by-step robotic technique for the surgical treatment of GBC and demonstrates the feasibility and safety of the robotic approach. More data and multicentre series are



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needed to confirm our results and to assess the oncologic outcomes of the robotic approach.

Keywords: Gallbladder cancer, robotic surgery, radical cholecystectomy, incidental gallbladder cancer, lymphadenectomy, minimally invasive surgery

INTRODUCTION

Minimally invasive approaches are gradually becoming a standard of care in abdominal surgical oncology. Several high-quality studies including randomized controlled trials demonstrated non-inferiority in terms of oncologic outcomes of the laparoscopic approach for the treatment of colorectal and gastric cancer and confirmed the advantages of minimal invasiveness in terms of perioperative outcomes and length of postoperative stay^[1-3]. The feasibility, safety and oncologic non-inferiority of laparoscopic liver resection have already been established as well as the advantages of the minimally invasive approach in terms of intraoperative bleeding and short-term outcomes^[4-7]. The minimally invasive approach to liver neoplasms is more and more applied worldwide and is becoming a routine approach in dedicated centres in selected patients for the surgical treatment of colorectal liver metastases and hepatocellular carcinoma^[4-7]. However, there is a strong reluctance to the adoption of the minimally invasive approach for the treatment of gallbladder cancer (GBC), which is one of the most aggressive cancers of the biliary tract and is generally associated with a poor prognosis. This scepticism is historically related to the fear of tumour dissemination due to bile spillage, tumour manipulation during laparoscopy, possible tumour peritoneal implantation due to the pneumoperitoneum as well as to technical difficulties related to liver resection and to the achievement of an adequate clearance of lymph nodes. Recently, some reports have advocated the minimally invasive surgical treatment of clinically suspected or incidentally diagnosed GBC, highlighting the feasibility and apparent safety of this approach^[8-13]. Nevertheless, only few authors have reported on the feasibility and outcomes of the surgical treatment of GBC by a robotic approach, which has the potential to facilitate, by the articulated instrumentations and magnified 3D view, the accomplishment of the procedure and the locoregional lymphadenectomy needed to obtain a radical resection and an accurate staging of the resected patients. The aim of this study was to report the outcomes of our initial experience with the robotic treatment of clinically suspected or incidentally diagnosed GBC and to highlight the technical details related to the robotic approach.

METHODS

This was a retrospective observational study including consecutive patients operated by a robotic approach for the surgical treatment of clinically suspected or incidentally diagnosed GBC (with the intent of radical re-resection after index cholecystectomy) at the National Cancer Institute - G. Pascale - IRCCS of Naples, Italy. Patients without relevant comorbidities precluding a minimally invasive approach were considered for robotic resection in case of the following.

- (1) A suspected preoperative diagnosis of GBC without massive liver involvement and/or suspicion of bile duct invasion (T stage > 1b and < T4) and no suspicion of peritoneal carcinomatosis.
- (2) Patients already submitted to cholecystectomy for presumed benign disease and an incidental diagnosis of GBC (T stage > 1b) without massive liver involvement and/or suspicion of bile duct invasion and no suspicion of peritoneal carcinomatosis.

The preoperative staging protocol included standard blood tests including carcinoembryonic antigen, carbohydrate antigen (CA) 19.9 and CA 125, a total-body CT scan and an abdominal MRI. An FDG-PET was used selectively in case of suspected advanced disease. Informed consent was obtained and patients

who refused the minimally invasive approach were offered a standard open operation. In case of a previous cholecystectomy, operative notes of the index gallbladder resection were carefully reviewed, and the surgeons who performed the operations were contacted whenever possible. Clinicopathological features of the patients were prospectively recorded in a dedicated electronic database and included age, sex, American Society of Anesthesiology score, previous abdominal surgery, tumour dimensions and T stage at preoperative imaging. Intraoperative variables analysed included operative time (divided into robotic system docking time and skin incision to skin closure time), occurrence and type of intraoperative complications, need and cause of conversion to laparoscopy or to laparotomy, blood loss, need for intraoperative transfusions, and occurrence of bile spillage. Surgery-related mortality was defined as death occurring during hospital admission or within 90 days of the operation. Occurrence of postoperative complications with 90 days were graded by the Clavien-Dindo classification^[14]. Specific morbidity related to lymphadenectomy was assessed in terms of biliary or vascular injuries, postoperative pancreatitis, bleeding and the occurrence of lymphatic fistula (defined as the presence of triglycerides in drain fluid > 110 mg/dL), bile leaks were graded by the definition of the International Study Group of Liver Surgery^[15]. Postoperative recorded variables included length of hospital stay, radicality of the resection (R1 resection defined as any microscopically positive margin or a cancer-free margin < 1 mm), T stage and number of retrieved and positive nodes at final pathology, M status, need for and accomplishment of postoperative chemotherapy. Oncologic follow-up included blood tests, tumour markers and a total-body CT scan at 40 days after the operation and at 3 and 6 months thereafter. Type and location of recurrence were prospectively recorded as well as the type of treatment administered when needed.

Surgical technique

Step 1

The patient is placed supine and legs apart in a slight reverse Trendelenburg and tilted to the left. A periumbilical incision is made, and the pneumoperitoneum is created by the open technique. Once the abdomen is insufflated, a staging laparoscopy is performed to exclude any sign of peritoneal carcinomatosis or diffuse hepatic involvement. In case of no contraindications to the procedure, 3 additional robotic trocars and one service 12-mm port for the assistant surgeon are inserted under direct view [Figure 1], and the robotic da Vinci Xi Surgical System® (Intuitive Surgical Inc. Sunnyvale, CA, USA) is docked. The first surgeon is at the robotic console while the assistant surgeon stands between the patient's legs.

Step 2

Intraoperative liver ultrasound is performed to assess the presence of liver invasion and its depth, and to exclude any other intrahepatic metastasis as well. In case of re-intervention after a previous cholecystectomy, any fatty or omental adhesions to the gallbladder bed are left in place with the aim of being resected *en bloc* with the liver resection specimen. The right colonic flexure is then mobilized and a wide Kocker manoeuvre is carried out to greatly expose the inferior vena cava and aorta. The lymph nodes of station 16 (aortocaval nodes) are excised from the gonadic vein caudally up to the left renal vein cranially by the aid of robotic scissors and robotic Maryland bipolar forceps and sent for frozen section analysis [Figure 2]. In case of node involvement the procedure is abandoned.

Step 3

Retropancreatic lymph nodes (i.e., station 13) are carefully excised avoiding injuries to the duodenum or the pancreatic head. This manoeuvre is facilitated by the 3D high-definition view of the surgical area and by the articulated robotic scissors and Maryland bipolar forceps [Figure 3]. The lymphadenectomy continues on the right lateral border of the hepatic pedicle (i.e., station 12). In case of re-intervention for revision post-cholecystectomy surgery at this level, even in the presence of inflammatory tissue, which can make the dissection difficult, an effort is made to isolate and resect the stump of the clipped cystic duct for frozen section analysis. In case of no previous cholecystectomy, Calot's triangle is dissected and the cystic duct

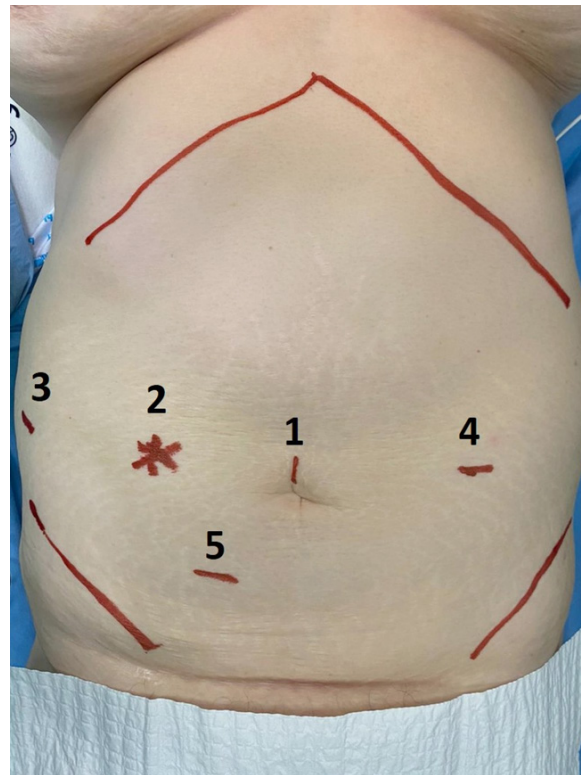


Figure 1. Sites for placement of trocars: (1) initial incision, robotic instrument and site for specimen extraction; (2) robotic optical system; (3) robotic instrument; (4) robotic instrument; and (5) laparoscopic port for assistant surgeon

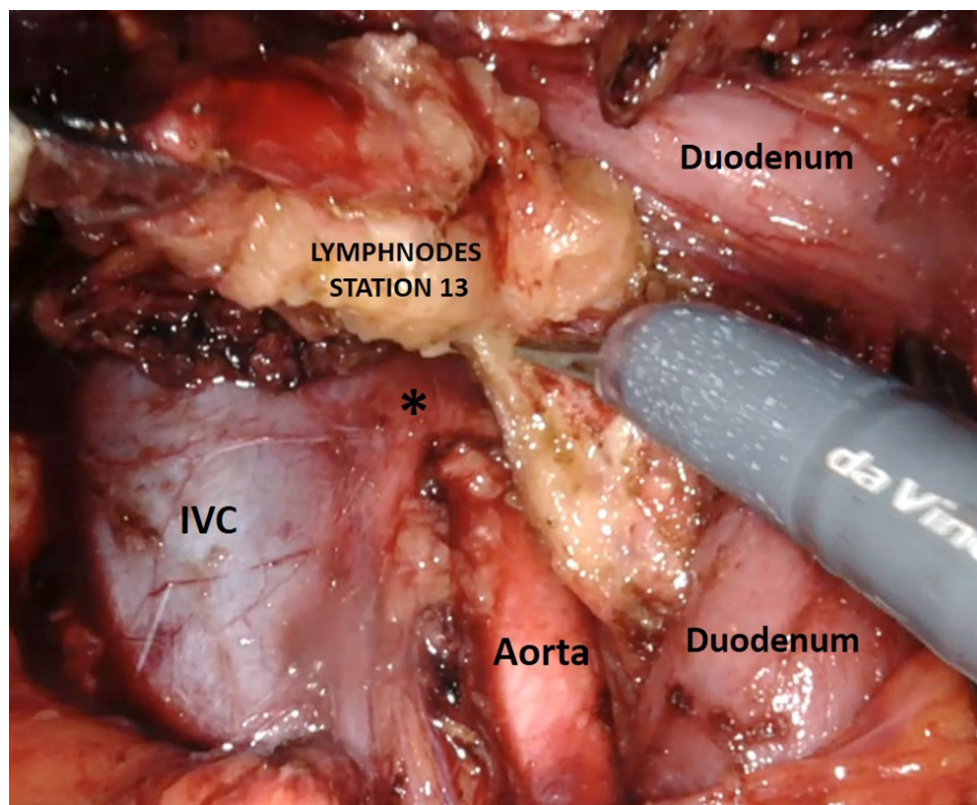


Figure 2. Intraoperative view of robotic retropancreatic lymphadenectomy. *Left renal vein. IVC: inferior vena cava

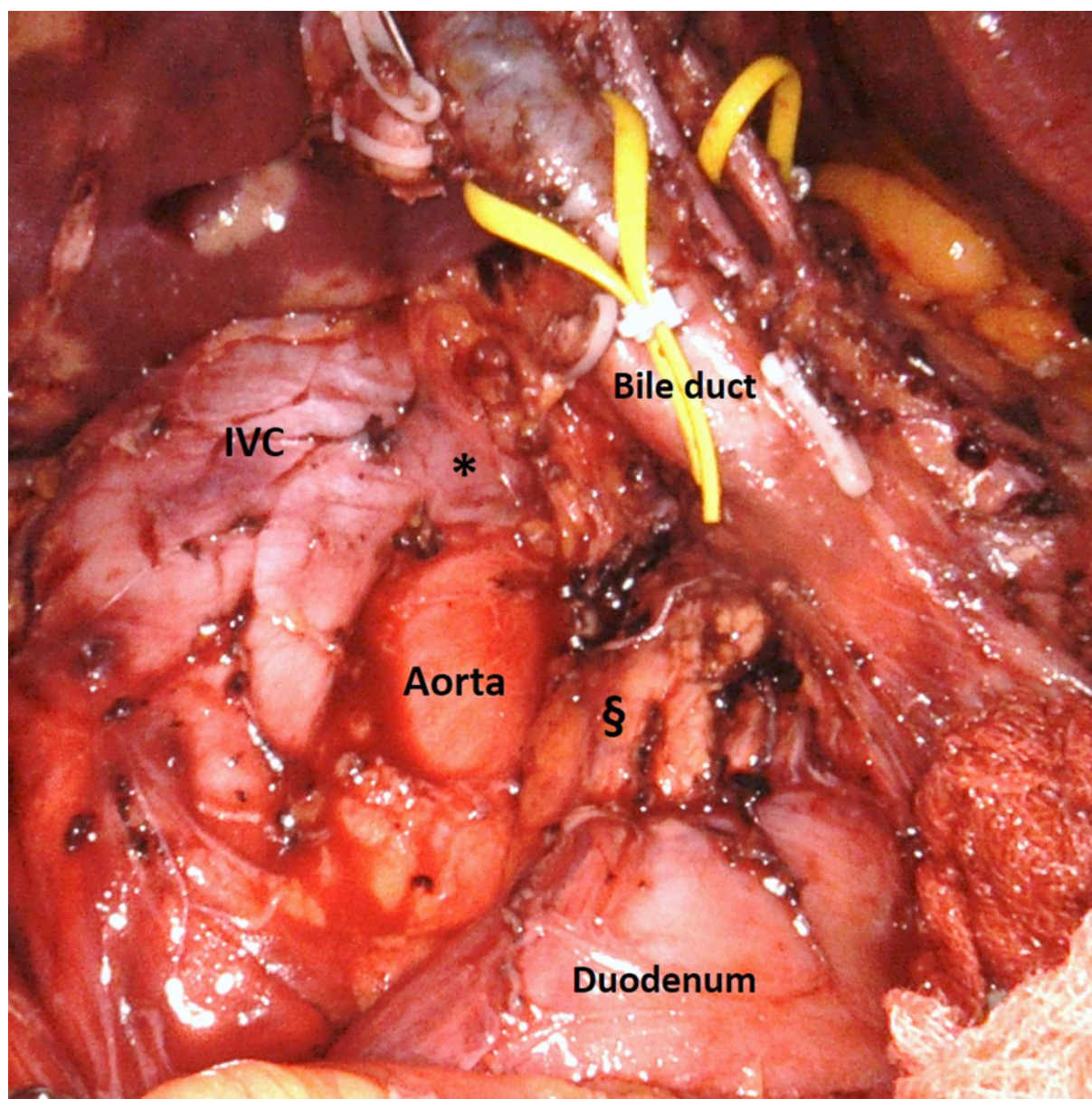


Figure 3. Final view after robotic lymphadenectomy. §Posterior aspect of pancreatic head; *left renal vein. IVC: inferior vena cava

and cystic artery are isolated and sectioned between clips. Retroportal soft tissue and the left side of the hepatoduodenal ligament are then dissected, and the structures of the portal triad skeletonized and hung on vessel loops [Figure 4]. This manoeuvre allows a complete clearance of station 9. The lymphadenectomy is completed by dissecting the proper and common hepatic artery (i.e., station 8), proceeding from the right to the left. Lymph nodes are finally collected ideally en-bloc and put in a plastic bag.

Step 4

The intended liver resection plane, which is tailored to the presence and the extent of tumour invasion into the parenchyma (a minimum of 2 cm in width wedge resection of segments IVb-V), is marked on the Glissonian surface with monopolar robotic scissors, and an ultrasound repeated to check the margin width and liver anatomy. Liver resection is then carried out (*en bloc* with the gallbladder when present) with the aid of moist robotic Maryland bipolar forceps and robotic vessel sealer. Any relevant biliary or

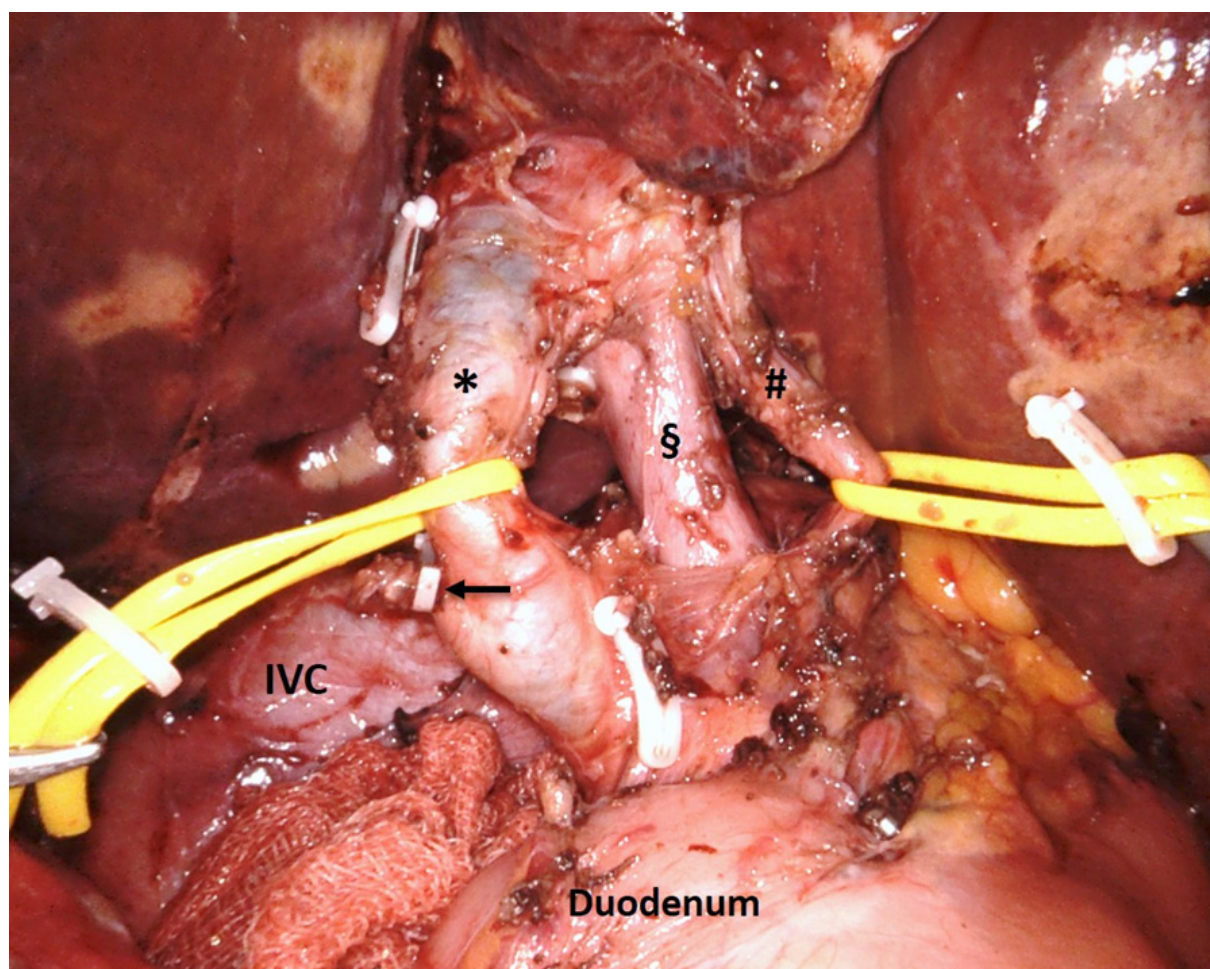


Figure 4. Final view after robotic lymphadenectomy of the hepatoduodenal ligament. *Bile duct; §portal vein; #hepatic artery; black arrow: stump of the cystic duct. IVC: inferior vena cava

vascular structures are carefully isolated and clipped to avoid postoperative bleeding or bile leaks. Once the resection is completed, the raw liver surface is further cauterized with robotic Maryland bipolar forceps [Figure 5] and haemostatic agents or patch can be applied on the resection bed at the surgeon's discretion. The liver specimen is placed in a plastic bag and a drain is placed under the cut liver with the tip under the hepatoduodenal ligament. Surgical specimens are extracted in plastic bags via a slightly enlarged periumbilical incision and the pneumoperitoneum aspirated.

RESULTS

Between January 2017 and December 2019, eight patients were operated by a robotic approach for a suspected preoperative diagnosis of GBC or for radicalisation after an incidental diagnosis of GBC at the National Cancer Institute - IRCCS Fondazione G. Pascale of Naples, Italy. Patient characteristics are given in Table 1. Four patients were female and four were male. The mean age of the patients was 70 years (range 42-89 years). Five patients were submitted to robotic radical cholecystectomy for suspected GBC, while three patients were submitted to radical revision surgery for an incidental diagnosis of GBC after index cholecystectomy. Pre- and postoperative tumour characteristics are described in Table 2. All patients were submitted to an extended lymphadenectomy plus a liver resection of the gallbladder bed (ultrasound-guided wedge resection of segment IVb-V with a minimum of 2-3 cm tumour-free margin). In all cases, the operation was successfully concluded by a robotic approach without the need for conversion to laparoscopic

Table 1. Patient characteristics

Patients	n/total (%)
Gender	
Male	4/8 (50%)
Female	4/8 (50%)
Age	
Years	70 (range 42-89)
ASA	
1	0/8 (0%)
2	2/8 (25%)
3	6/8 (75%)
4	0/8 (0%)
Previous cholecystectomy	
Yes	3/8 (37.5%)
No	5/8 (62.5%)
Previous abdominal surgery	
Yes	5/8 (62.5%)
No	3/8 (37.5%)

ASA: American Society of Anesthesiology

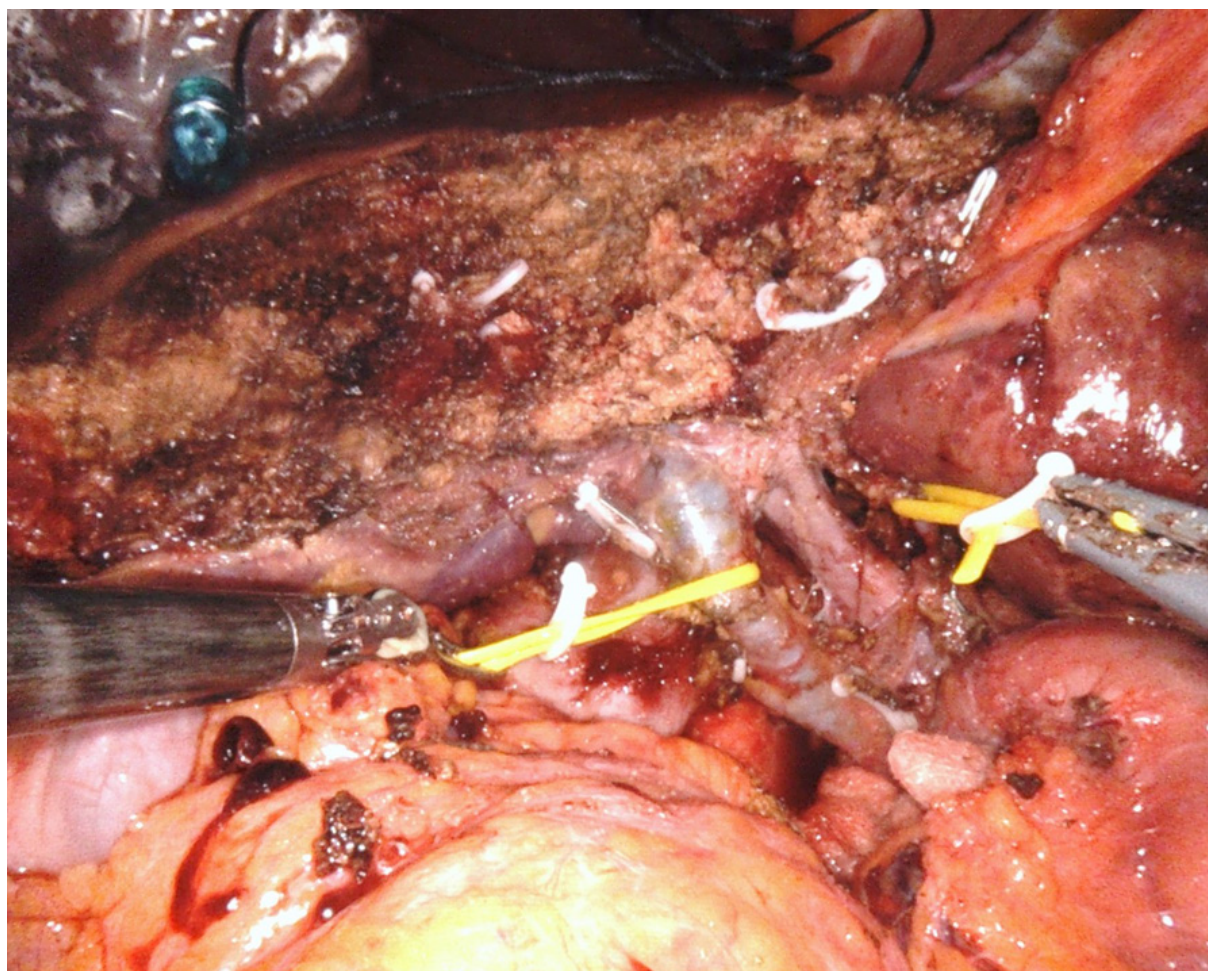
**Figure 5.** Final intraoperative view at the end of the procedure of radical cholecystectomy (including atypical resection of liver segments IVb-V)

Table 2. Pre- and postoperative tumour characteristics

Incidental GBC (3 patients)		Suspected GBC (5 patients)
Preoperative tumour size		
No evidence of liver mass		19.6 mm (range 12-31 mm)
Preoperative T stage		
T1b	2/3 (66.6%)	1/5 (20%)
T2a	1/3 (33.3%)	0/5 (0%)
T2b	0/3 (0%)	2/5 (40%)
T3	0/3 (0%)	2/5 (40%)
Postoperative T stage		
T1b	2/3 (66.6%)	1/5 (20%)
T2a	1/3 (33.3%)	0/5 (0%)
T2b	0/3 (0%)	1/5 (20%)
T3	0/3 (0%)	3/5 (60%)
Lymph node status		
N0	2/3 (66.6%)	4/5 (80%)
N+	1/3 (33.3%)	1/5 (20%)
Total lymph nodes		
1-6	0/3 (0%)	0/5 (0%)
7-12	1/3 (33.3%)	1/5 (20%)
> 12	2/3 (66.6%)	4/5 (80%)
Mean	22.35 ± 1.75	25.75 ± 2.25

GBC: gallbladder cancer

or open surgery. In one case, minor intraoperative bleeding from the inferior vena cava occurred during lymphadenectomy and was effectively managed by robotic suturing with prolene 3/0 stiches. Operative time was 46.25 min (range 30-70 min) for robot docking time and adhesiolysis (5 patients having extensive adhesions due to previous laparotomic abdominal surgery) and 147.5 min (range 110-220 min) for robotic accomplishment of radical cholecystectomy. Mean blood loss was 198.75 mL (range 50-600 mL) and no intraoperative transfusions were needed. No bile leaks nor lymphatic fistula occurred. Mean postoperative stay was 6 days (range 5-11 days). Postoperative morbidity included one postoperative bleeding treated with a transfusion of packed red blood cell (Clavien-Dindo grade II complication) and one re-intervention for a strangulated bowel loop herniated at one of the trocar site (Clavien-Dindo grade IIIb complication). All patients had an R0 liver resection and 2 patients had N positive disease at final pathology. Mean lymph nodes yield was 25.75 ± 2.25 , and all patients had more than 6 retrieved lymph nodes. Intraoperative and postoperative information is provided in Table 3. The cystic duct margin was negative in all patients as well as the station 16 sampling for frozen section analysis. With a mean follow-up of 17.5 months (range 29.3-7.3 months), all patients are alive and all but one, who experienced a peritoneal recurrence and is currently undergoing chemotherapy, are free from disease and under clinical follow-up. No port site metastases were observed during the follow-up period.

DISCUSSION

The current study is one of the very few reported series on the robotic approach to the surgical treatment of GBC. We presented a prospective series of eight consecutive patients operated for GBC by a robotic approach with results comparable to those reported in the recent literature and showed the feasibility and the safety of this minimally invasive approach. Despite that cholecystectomy was the first surgical intervention widely performed by laparoscopy, a strong reluctance accompanied the adoption of the minimally invasive approach for the treatment of GBC, which is one of the most aggressive cancers of the biliary tract and is generally associated with a poor prognosis. One of the major concerns related to the adoption of the minimally invasive approach for GBC has been the fear of port site recurrence, which has been historically reported to occur in up to 18.6% of cases in the case of incidental GBC^[16]. Tumour cell implantation at the port sites is postulated to occur by extraction of surgical specimen without protective

Table 3. Intraoperative and postoperative information

Robot docking time + adhesiolysis	46.25 min (range 30-70)
Robotic radical cholecystectomy operative time	147.5 min (range 110-220)
Intraoperative blood loss	198.75 mL (range 50-600)
Intraoperative complications	
Bleeding	1/8 (12.5%)
Conversion rate	0/8 (0%)
Postoperative complications	
Bleeding	1/8 (12.5%)
Ventral hernia on port defect	1/8 (12.5%)
Hospital stay	6 days (range 5-11)
Follow-up	
Mean	17.5 months (range 29.3-7.3)

bag, contact with contaminated instruments (especially in case of bile spillage) or by nidation of exfoliated tumour cells brought to the port site by a sort of aerosol effect created by desufflation of the pneumoperitoneum. The historically reported data are perhaps related to an inappropriate surgical technique carried out in the early years of the learning curve of laparoscopic cholecystectomy for presumed benign disease and were probably associated with gallbladder perforation, bile spillage and no use of protective bag for specimen extraction. The key role of bile spillage during index cholecystectomy for incidentally diagnosed GBC has been addressed in a population-based study by Horkoff *et al.*^[17] who highlighted in a retrospective cohort comparison the negative prognostic impact of bile spillage and its role in the development of peritoneal carcinomatosis. The occurrence of incidentally diagnosed GBC after cholecystectomy is assumed to vary between 0.19% and 3.3%^[18] with a slight increase after the advent of laparoscopic cholecystectomy. Generally, simple cholecystectomy is considered an adequate treatment for Tis and T1a cancers while a re-intervention consisting in a radical cholecystectomy as first described by Glenn and Hays^[19] (which includes locoregional lymphadenectomy and gallbladder bed liver resection) is suggested to resect any potential residual disease and obtain an adequate staging. Since cholecystectomy has already been performed, revision surgery for incidentally diagnosed GBC is not at risk of tumour seeding associated with bile spillage. Full-thickness resection of the port insertion sites at index cholecystectomy has been advocated to minimize the incidence of port site recurrence^[20], but as demonstrated by Maker *et al.*^[21] port site resection is not associated with improved survival or disease recurrence and should not be considered mandatory. Nevertheless, radical revision surgery can be very technically demanding because of the presence of fibrosis and inflammatory adhesions often present in the gallbladder bed and at the hepatoduodenal ligament, thus complicating the identification of the vasculo-biliary structures and the risk of bile duct injury during radical lymphadenectomy. Only in the last decade, some authors have advocated the minimally invasive surgical treatment of clinically suspected or incidentally diagnosed GBC, highlighting the feasibility and apparent safety of this approach in terms of oncologic outcomes. In 2011, Belli *et al.*^[8] published their initial series of patients with incidental GBC who underwent a revision procedure by a totally laparoscopic approach, reporting satisfactory clinical outcomes in terms of perioperative and middle term oncologic results. Recently, Vega *et al.*^[9] reported the results of a multicentre retrospective study of patients with incidental GBC who underwent re-resection with curative intent at four centres (including 65 patients operated by a laparoscopic approach) and concluded that a laparoscopic approach for radical re-resection has similar morbidity and oncologic outcomes as open radical re-resection. Feng *et al.*^[10] conducted a comparative analysis of open (61 patients) versus laparoscopic (41 patients) cholecystectomy and radical cholecystectomy for Tis-T3 GBC and found no differences between the two approaches in terms of lymph node retrieval and survival outcomes. Similar results were reported in the retrospective comparative series (open vs. laparoscopic approach) published by Jang *et al.*^[11] and Dou *et al.*^[12] In the study by Agarwal *et al.*^[13], also analysed in a retrospective comparative design were the outcomes of GBC patients (with limited liver infiltration or incidental diagnosis) who underwent laparoscopic radical resection versus those of patients who underwent open radical

cholecystectomy during the same period. They concluded that laparoscopic radical cholecystectomy is safe and feasible in selected patients with GBC and can offer similar results as open approach. An expert consensus statement published in 2019 recognises that the laparoscopic approach to GBC seems to have favourable outcomes in selected cases operated by expert teams^[22] but also highlights that the minimally invasive approach for GBC is still in the early phase of the adoption curve, and more data are needed to assess the outcomes of the procedure. Only anecdotal reports on the surgical treatment of GBC by a robotic approach are currently available in the literature. Byun *et al.*^[23] described their robotic technique for the resection of 13 patients with T2 or greater stage GBC and highlighted the feasibility and safety of the robotic approach and adequate lymph node retrieval. Goel *et al.*^[24] compared the operative outcomes of 23 patients submitted to robotic radical cholecystectomy to those of 70 patients submitted to open procedure and reported a 14.8% conversion rate and equivalent oncologic and perioperative outcomes between the two approaches. There is no consensus on the extent of optimal lymphadenectomy for GBC, but in the authors' opinion, a full locoregional node clearance including retro-pancreatic nodes should be performed together with intraaortocaval sampling (station 16b1). In fact, as demonstrated by Agarwal *et al.*^[25], routine sampling at this level prevents non-therapeutic radical resection in 18.6% of patients deemed resectable on preoperative imaging and staging laparoscopy. The minimum number of harvested nodes for GBC is still a matter of debate, where the 8th edition of the AJCC^[26] recommends a cut-off of six retrieved nodes for GBC. In our series, all patients had more than 6 lymph nodes retrieved, which is in line with the results of reported open series and fulfil the benchmarks proposed by the AJCC. Radical extended cholecystectomy or radicalisation of incidentally GBC can be technically demanding procedures consisting in a liver resection and an accurate lymphadenectomy, including the retropancreatic nodes and a full clearance of the hepatoduodenal ligament, which requires a high grade of dexterity when performed by unidirectional instruments as in laparoscopy. Appropriate lymphadenectomy can be performed safely and effectively by laparoscopy as demonstrated by Ratti *et al.*^[27], but it deserves advanced laparoscopic skills and a suitable learning curve. In our opinion, the application of the robotic platform in this settings, thanks to higher dexterity achievable with the robotic instruments, which with the endowrist system have seven degrees of freedom, can facilitate adequate surgical manipulation and the achievement of an appropriate lymph node clearance in a confined space such as the hepatic pedicle. The magnified high-resolution 3D stereoscopic view offered by the robotic platform is also an added value in defining the anatomical structures. As regards to the extent of liver resection for GBC, there is still no broad consensus, and parenchymal resection is generally tailored on T stage and tumour size and location^[28,29]. While for T1b and T2 cancers, an extended cholecystectomy (atypical resection of segment IVb-V or a formal bisegmentectomy) is generally considered adequate, but the optimal extent of liver resection for T3 tumours is still unclear. Since GBC is staged as T3 by the AJCC for any infiltration of liver parenchyma, regardless of the location and size of the tumour, the surgical treatment can vary widely from an ultrasound-guided atypical resection (for liver bed type tumours located at the gallbladder fundus) to up a formal extended hemi-hepatectomy (generally reserved for T3 gallbladder neck and hepatic hilum type tumours). In our series, we decided on a robotic approach only in patients with liver bed type lesions of the gallbladder fundus and a limited liver involvement [mean tumour size of 19.6 mm (range 12-31 mm)], and therefore we considered appropriate an atypical resection of segments IVb-V with a an ultrasound-checked free margin of at least 2-3 cm^[30]. Such as for laparoscopy, the robotic approach when compared to the standard open approach, which requires a wide bilateral subcostal incision, can promote a faster recovery, as demonstrated by the short postoperative stay of our series, and a fast access to adjuvant chemotherapy when appropriate. This an important issue in a biologically aggressive disease such as GBC and could play a role in prolonging survival. As regards to early oncologic outcomes, no port site metastases were observed during the follow-up period in the current series. One of our patients experienced an early peritoneal recurrence, but this is more likely to be related to the advanced stage of the disease (T2 N1) and to the adenosquamous histological type of the cancer than to any factor related to the surgical approach. This is one of the very few reports currently available in the literature on the robotic treatment of GBC. Our series is limited and

needs further evaluation especially in terms of oncologic outcomes, but we did demonstrate the safety and technical feasibility of the robotic approach for the treatment of selected GBC. With an accurate patient selection, a low threshold for conversion and a proper surgical technique which includes careful tissue manipulation, the avoidance of any bile spillage, an adequate locoregional lymphadenectomy and the use of a protective plastic bag for specimen extraction, similar outcomes as with open surgery can be offered by a robotic approach. In addition, the use of the robotic platform has the potential to facilitate the surgical procedure when compared to laparoscopy, speed up the learning curve and maintain the benefits of better short-term outcomes and rapid recovery associated with minimally invasive surgery.

In conclusion, our study described a standardized step-by-step robotic technique for the surgical treatment of clinically suspected or incidentally diagnosed GBC and demonstrated the feasibility and the safety of the robotic approach in this setting. More data and multicentre series are needed to confirm our results and to assess the oncologic outcomes of the robotic approach.

DECLARATIONS

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Authors' contributions

Conception and design: Belli A, Patrone R, Izzo F

Manuscript writing, collection and assembly of data, data analysis and interpretation: Belli A, Patrone R

Provision of study materials or patients, critical revision and final approval of manuscript: Belli A, Patrone R, Albino V, Leongito M, Piccirillo M, Granata V, Pasta G, Palaia R, Izzo F

Availability of data and materials

Data are stored in a database at Fondazione G. Pascale IRCCS Naples.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study was approved by the local ethics committee. The informed consent to participate of patients was obtained.

Consent for publication

The informed consent for publication of patients was obtained.

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Review

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3D printing applications for percutaneous structural interventions in congenital heart disease

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Abstract

The past several decades have seen remarkable advancements in percutaneous interventions for treatment of congenital heart disease (CHD). These advancements have been significantly aided by improvements in noninvasive diagnostic imaging. The use of three-dimensional (3D) printed models for planning and simulation of catheter-based procedures has been demonstrated for numerous cardiac defects and has been shown to reduce complications, procedure times, and limit radiation exposure. This paper reviews the process by which patient-specific 3D cardiac models are produced, as well as numerous applications of these models for use in percutaneous interventions in CHD.

Keywords: 3D models, pediatric interventional cardiology, congenital heart disease

INTRODUCTION

Over the past several decades, there has been a tremendous reduction in the morbidity and mortality associated with congenital heart disease (CHD) treatment. The wide array of anatomic pathologies can make diagnosis and management of these defects particularly challenging. Advances in the therapies for CHD have been aided largely by improvements in noninvasive diagnostic imaging. Traditional echocardiography demonstrates cardiac anatomy in two-dimensional (2D) planes, thereby limiting one's ability to fully visualize complex intracardiac structures and spatial relationships. While three-dimensional



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(3D) printing has been in use since the 1980s, recent application of this technique to the field of CHD has aided in both diagnosis of cardiac defects and pre-procedural planning, and has been shown to be particularly beneficial in guiding treatment of patients with more complex intracardiac anatomy^[1-4].

3D reconstruction of imaging data from computed tomography (CT), magnetic resonance imaging (MRI), and 3D echocardiography allows for enhanced understanding of complex intracardiac anatomy prior to surgical or catheter-based procedures^[5]. 3D models have been shown to be especially useful in devising percutaneous interventions for treatment of CHD. In recent years, there has been a remarkable evolution of catheterization techniques and technologies, including the development of numerous minimally invasive techniques to treat patients with CHD^[3,6]. Catheter-based interventions have become the standard of care for a variety of procedures involving valve pathology, septal defects, and vascular abnormalities^[6]. 3D models have the potential to provide additional anatomic insight and can be used to mimic device or stent implantations prior to the procedure. This is particularly useful for interventional cardiac procedures, as 3D models can be used to ascertain optimal shape and size of the device, understand how the device will fit into a specified location, and simulate the procedure in order to determine the optimal approach^[1,2]. These models also enable proceduralists to perform entire procedures beforehand, thereby providing a means to anticipate complications, reduce radiation exposure, and potentially improve patient outcomes^[5]. Here, we discuss the process by which patient-specific 3D cardiac models are produced, as well as numerous applications of these models for use in percutaneous interventions in CHD.

IMAGE POSTPROCESSING

Prior to creating a 3D model, a volumetric imaging dataset is acquired. CT and MRI are the most commonly used modalities for creating 3D reconstructions, although echocardiography and rotational angiography have also been used^[5]. Preference of one modality over another depends largely on the experience of the center, the structure of interest, and age of patient. CT has been shown to be the easiest modality for model creation as it allows for particularly detailed segmentation of great vessels and intracardiac anatomy due to high spatial resolution^[5]. Alternatively, MRI or contrast-enhanced magnetic resonance angiography offers whole heart 3D datasets while avoiding radiation exposure, which is preferred in younger patients^[1]. More recently, there have been several reports on the use of 3D echocardiography in creating 3D reconstructions. Novel echocardiographic transducers as well as advancements in software and hardware have enhanced echocardiographic images, making them more suited for 3D modeling^[7]. The use of echocardiography is beneficial as it is more widely available and avoids both radiation exposure and the necessity of radiocontrast administration^[1]. This modality, however, has an inferior tissue-to-blood pool contrast, which makes image segmentation significantly more challenging. Echocardiography is also the preferred means by which to visualize cardiac valves and the atrial septum, which are poorly delineated in both CT and MRI. Hybrid imaging techniques have also been developed, which combine cross-sectional datasets with ultrasound in order to create complete heart models with embedded valve leaflets for more comprehensive visualization of intracardiac anatomy^[2,7].

Following the acquisition of the imaging dataset, a 3D rendering is created through a process known as segmentation^[8]. The files are first uploaded as a DICOM (Digital Imaging and Communications in Medicine) dataset into 3D visualization software, such as Mimics (Materialise, Belgium), or open-source software, such as 3D Slicer (Slicer Wiki). Pixel-intensity-based thresholding is then employed to highlight the blood pool within the desired region. Subsequently, regions of interest are isolated through manual or semi-automatic techniques. The process of segmentation is the most time-consuming step of creating a 3D reconstruction. Accuracy of the model is largely determined by blood pool-to-tissue contrast, spatial resolution of the imaging technique, motion artifact of the image, and the technician's understanding of anatomic relationships^[1,8]. The 3D rendering is then imported as a stereolithography (stl) file into a 3D visualization software, such as 3-Matic (Materialise, Belgium), or open source programs, such as Blender

or Owlet, for post-processing to establish a print-compatible model^[1,8]. This process involves converting the object into a meshed surface file, hollowing the model, smoothing surfaces, and trimming vessels or chamber walls in order to visualize the area of interest^[5]. The 3D rendered object is converted into a computer-aided design format that can be converted into a physical object using a 3D printer^[8].

Once complete, the 3D rendering undergoes rapid prototyping on a 3D printer. Capabilities of 3D printers vary based on build volume, layer resolution, materials, and colors available^[9]. The print technology utilized should be chosen based on the specific goal of the heart model. In making this decision, the material needed, level of detail, and turnaround time are all taken into consideration. Options for 3D printing include fused deposition modeling (FDM), Colorjet, Polyjet printing, and selective laser sintering^[1]. In FDM, a thermoplastic filament is extruded in a specified pattern that immediately hardens. This process typically has a shorter turnaround time and comes at a significantly lower cost^[8]. Colorjet printing is an additive manufacturing technology in which a core material is spread in thin layers and solidified by extrusion of a color binder. This technology allows for recreation of highly complex geometries in relatively short production times^[10]. Polyjet printing, in contrast, allows for higher resolution printing of multiple materials in different colors, but it is much more costly and thus less often employed for routine modeling^[7]. This technique enables the use of flexible, translucent materials, which are optimal for rehearsing surgical procedures as they can be cut, retracted, and sutured in order to effectively simulate procedures^[1]. Additionally, selective laser sintering utilizes a high-power laser to fuse metal or ceramic powder, resulting in a highly accurate model. This method, however, is often cost prohibitive in comparison to other techniques^[5]. For each technique, the print material is sequentially layered, and the final model is encased in support material, which can be removed manually or by soaking in a solution^[9].

CLINICAL APPLICATIONS

The use of 3D printed models has been described widely for numerous percutaneous interventions for the treatment of CHD. One of the most well described interventions in which 3D models play a role is transcatheter valve implantation. These procedures represent the fastest growing area of innovation in the field of pediatric interventional cardiology, with numerous devices developed in the last decade^[8]. Transcatheter valve replacements are beneficial because they enable proceduralists to correct valve regurgitation or stenosis without the need for repeat surgical interventions over the course of the patient's life^[2,11]. Among these procedures, pulmonary valve replacement in repaired cases of Tetralogy of Fallot and aortic valve replacement for aortic stenosis or regurgitation are the most widely described. Poterucha *et al.*^[12] described a case of repaired tetralogy of Fallot in which the native right ventricular outflow tract (RVOT) was deemed to be unfavorable for percutaneous intervention. A 3D model of the RVOT [Figure 1] was then developed using 3D rotational angiography, which helped the interventionalist identify a landing zone for implantation of a Melody Valve (Medtronic, Fridley, Minnesota). A study by Shievano and colleagues showed that the use of 3D printed models allowed for more accurate selection of candidates for successful percutaneous pulmonary valve implantation (PPVI) than 3D MRI reconstructions alone^[13]. Qian *et al.*^[14] demonstrated the use of 3D printed models of the left ventricular outflow tract (LVOT) and aortic root of patients with aortic stenosis. The models approximated the precise anatomy and flexibility of the LVOT, which had substantial tissue calcifications, and were used to test valve implantation prior to the procedure. This permitted the proceduralists to assess the feasibility of the intervention and predict paravalvular leak after transcatheter aortic valve replacement^[9,14]. To test paravalvular leak, the models underwent analysis of strain distribution using a maximum bulge index, which aided in prediction of the degree of leakage following percutaneous valve implantation. This technique ultimately assisted in identifying ideal candidates for percutaneous rather than surgical intervention^[14]. Along the same lines, Ripley *et al.*^[15] studied the use of 3D models to replicate patient-specific aortic root anatomy prior to transcatheter aortic valve replacement, and they found that the models provide insight into how the patient anatomy will interact with implanted medical devices. This enables interventionalists to predict potential challenges in device placement and complications during or following the procedure.

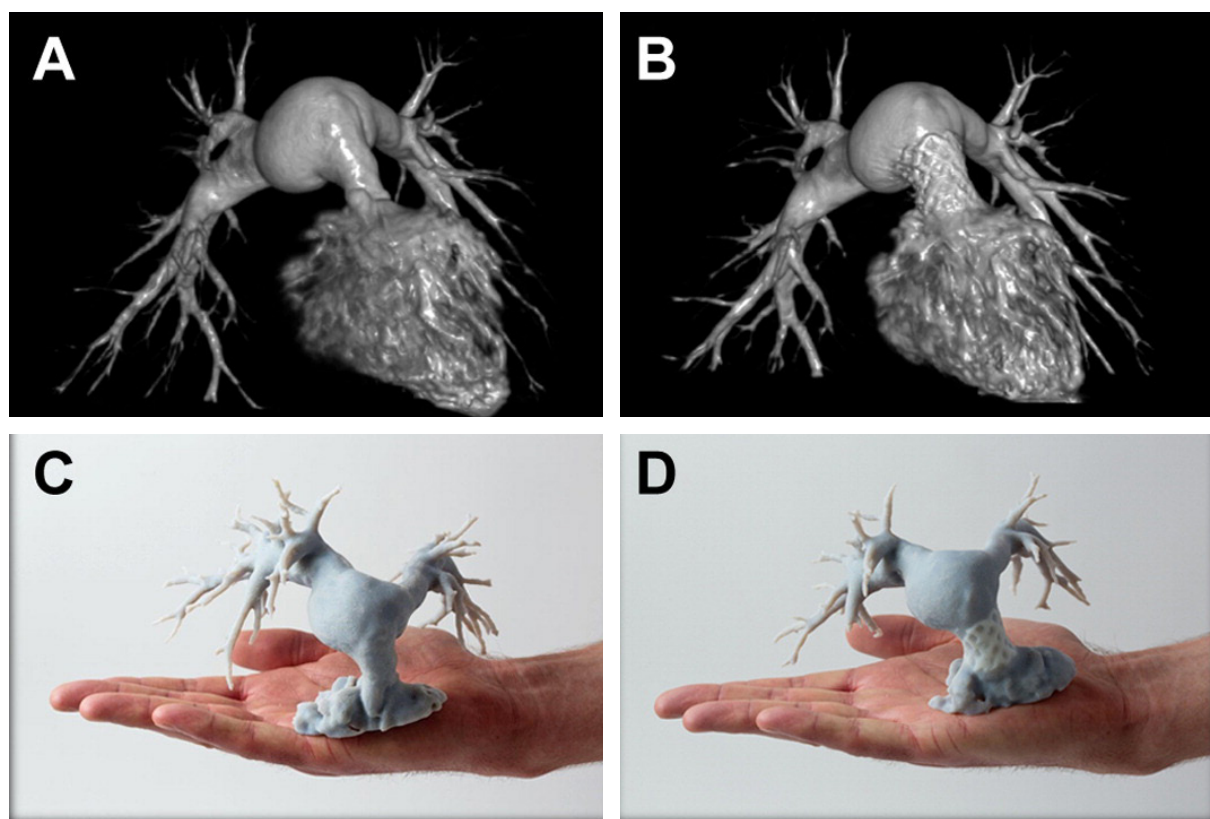


Figure 1. 3D DynaCT reconstruction and 3D printed models: pre-Melody valve implantation in the RVOT (A, C); and post-Melody valve implantation in the RVOT (B, D). Reprinted with permission from Poterucha *et al.*^[12]. 3D: three-dimensional; RVOT: right ventricular outflow tract

An increasing number of devices have become available for atrioventricular valve repair using a percutaneous approach. Little *et al.*^[16] reported a case in which a 3D printed model was used to aid in procedural planning for a patient undergoing mitral valve repair with Mitraclip (Abbott, Abbott Park, Illinois). This group printed a multi-material 3D model in order to produce more realistic, deformable valve leaflets and recreate subvalvular calcium deposits within the adjacent myocardium. The model was then used to aid in the selection and sizing of the specific clip [Figure 2]. It enabled more accurate determination of a landing point for the device that avoided adjacent calcified tissue, and provided direct visualization of the effect of the implant on surrounding valve morphology and function^[16]. Scanlan and colleagues performed a study in which patient-specific pediatric atrioventricular valves were modeled from 3D echocardiography^[17]. The valves were printed and molded using custom software. The molded silicone valves were shown to be significantly more realistic for cutting and suturing, thus enhancing pre-procedural simulation. The technique is presently too time and labor intensive for widespread implementation^[17].

3D printed models are commonly used as guides for percutaneous closure of complicated atrial and ventricular septal defects. Velasco Forte *et al.*^[18] described a case in which a flexible, translucent 3D model was developed from a cardiac MRI in order to simulate the correction of a sinus venosus atrial septal defect (ASD). The model in this case allowed the interventionalists to accurately assess the anatomy and precise spatial relationships among the superior vena cava (SVC), left atrium (LA), and an anomalous pulmonary vein (PV). The model was also used to determine the length of the stent required to close the defect and assess the positioning of the stent necessary to redirect blood flow from the anomalous PV to the LA without obstructing flow from other vessels [Figure 3]. Ultimately, a custom stent was successfully implanted into the SVC to close the sinus venosus ASD and commit the anomalous PV drainage correctly to the LA^[18].

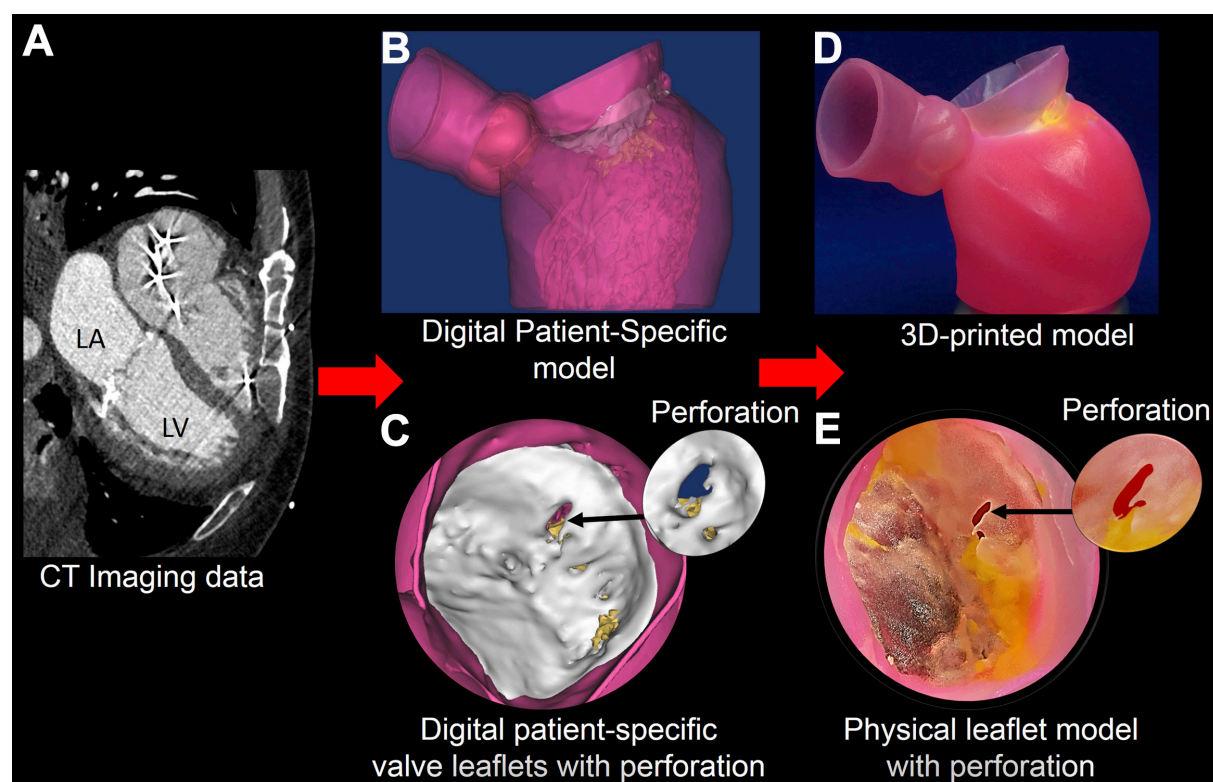


Figure 2. CT images (A) are used to create a digital model (B) and to assign tissue properties (C); the multi-material patient-specific 3D model (D, E) is then printed to replicate the mitral valve leaflet geometry, regional calcium deposition, and pathology. Reprinted with permission from Little *et al.*^[16]. CT: computed tomography; 3D: three-dimensional

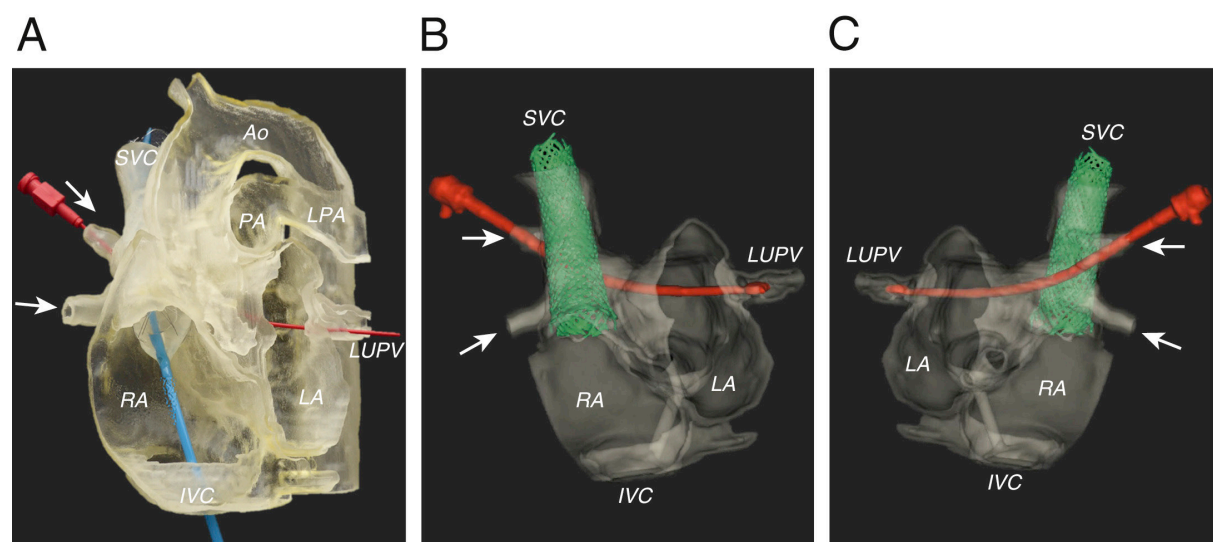


Figure 3. The flexible, translucent model (A) was examined to assess the relationship of the anomalous PVs (arrows) to the SVC and LA. A balloon-mounted stent catheter was placed in the SVC to RA junction (blue catheter), while a dilator (red) was passed from the anomalous right upper PV to the left upper PV. This model allowed for calculation of the length of the stent required to close the defect and redirect the flow of the partial anomalous pulmonary venous drainage toward the LA. CT of the model was performed using 3D rotational X-ray acquisition, shown from anteroposterior (B) and postero-anterior views (C) (dilator in red; stent in green). Reprinted with permission from Velasco Forte *et al.*^[18]. PV: pulmonary vein; SVC: superior vena cava; LA: left atrium; RA: right atrium; CT: computed tomography; 3D: three-dimensional

Another technically challenging percutaneous intervention that has the potential to be enhanced by patient-specific 3D printed models is endovascular stenting of the aorta in cases of aortic hypoplasia or coarctation. Placement of a stent within the aorta can result in many complications including stent migration, stroke, and occlusion of head and neck vessels by the stent itself. Valverde *et al.*^[19] presented a case in which a 3D model of a hypoplastic transverse aortic arch was created that closely mimicked the distensibility of the native vasculature and its response to stent delivery. In the case described, the endovascular stenting procedure was simulated on the printed model under fluoroscopic guidance prior to the percutaneous intervention. This simulation provided the proceduralists the opportunity to devise an optimal interventional approach, as well as determine the appropriate stent size, length, and position within the aorta^[19].

3D printed models have recently been described for use in patients undergoing left atrial appendage (LAA) closure. Occlusion of the LAA in patients with atrial fibrillation significantly reduces thromboembolic risk in those who have contraindications to systemic anticoagulation^[20]. Given the variable dimensions and morphology of the LAA, accurately sizing and positioning an occluder device in the orifice of the LAA can be challenging. Additionally, implanting a sub-optimally sized device to occlude the orifice can result in complications such as peri-device leakage, thrombus formation, device migration, and cardiac injury. Fan *et al.*^[20] conducted a study assessing the utility of 3D printed models created from 3D trans-esophageal echocardiography to aid in the selection of an appropriately sized device [Figure 4]. They found that device sizing based on 3D-printed models was associated with higher implantation success, shorter procedural times, and fewer complications. Iriart *et al.*^[21] described their technique of printing the entire left atrium and atrial septum in addition to the LAA in order to determine the optimal orientation for transseptal puncture during device placement. They also found that the models are invaluable in training physicians and fellows and augmenting communication with patients^[21].

Percutaneous closure of patent ductus arteriosus (PDA) is another intervention that has the potential to benefit from the use of 3D printed models. Particularly in adult cases, the PDA can be long, tortuous, and calcified, which makes catheter-based device placement challenging. Matsubara and colleagues presented a case in which patient-specific 3D printed models were created to detail the precise anatomy of the proximal aorta, aortic arch, PDA, and pulmonary artery^[22]. These models allowed for selection of a particular device and exact size. They also allowed the interventionalists to simulate and practice device deployment within the models themselves, thereby decreasing fluoroscopic and procedural times^[22].

3D models can be instrumental in decision making to determine feasibility of transcatheter intervention. A recent case at our center involved a 78-year-old patient with a sinus venosus atrial septal defect with partial anomalous pulmonary venous return of the right upper pulmonary vein (RUPV) to the superior vena cava. A 3D model was created from a cardiac CT to demonstrate the relationship between the anomalous pulmonary venous return, atrial communication, and left atrium for potential use of a covered stent to reroute the RUPV flow. Although the cross-sectional imaging was helpful in delineating the pulmonary venous anatomy, the 3D model provided a much clearer picture of the spatial relationship among the RUPV, superior vena cava, and the left atrium. It was determined that use of a covered stent would result in occlusion of the RUPV in the position needed to ensure stent stability and avoid embolization. The patient will undergo surgical intervention for this congenital heart defect.

Finally, We described a case in which a large fistula, arising from the left coronary artery to the right atrium, was modeled in order to devise an approach for interventional closure [Figure 5A and B]. The 3D printed model enabled the interventionalists to consider several different approaches to transcatheter closure of the fistula [Figure 6]. Practicing the device closure on the 3D model demonstrated the feasibility of using a venous approach to access the fistula and provided insight on the optimal device to use for the procedure, with the goal of ultimately limiting procedure time and thereby reducing radiation exposure^[23].

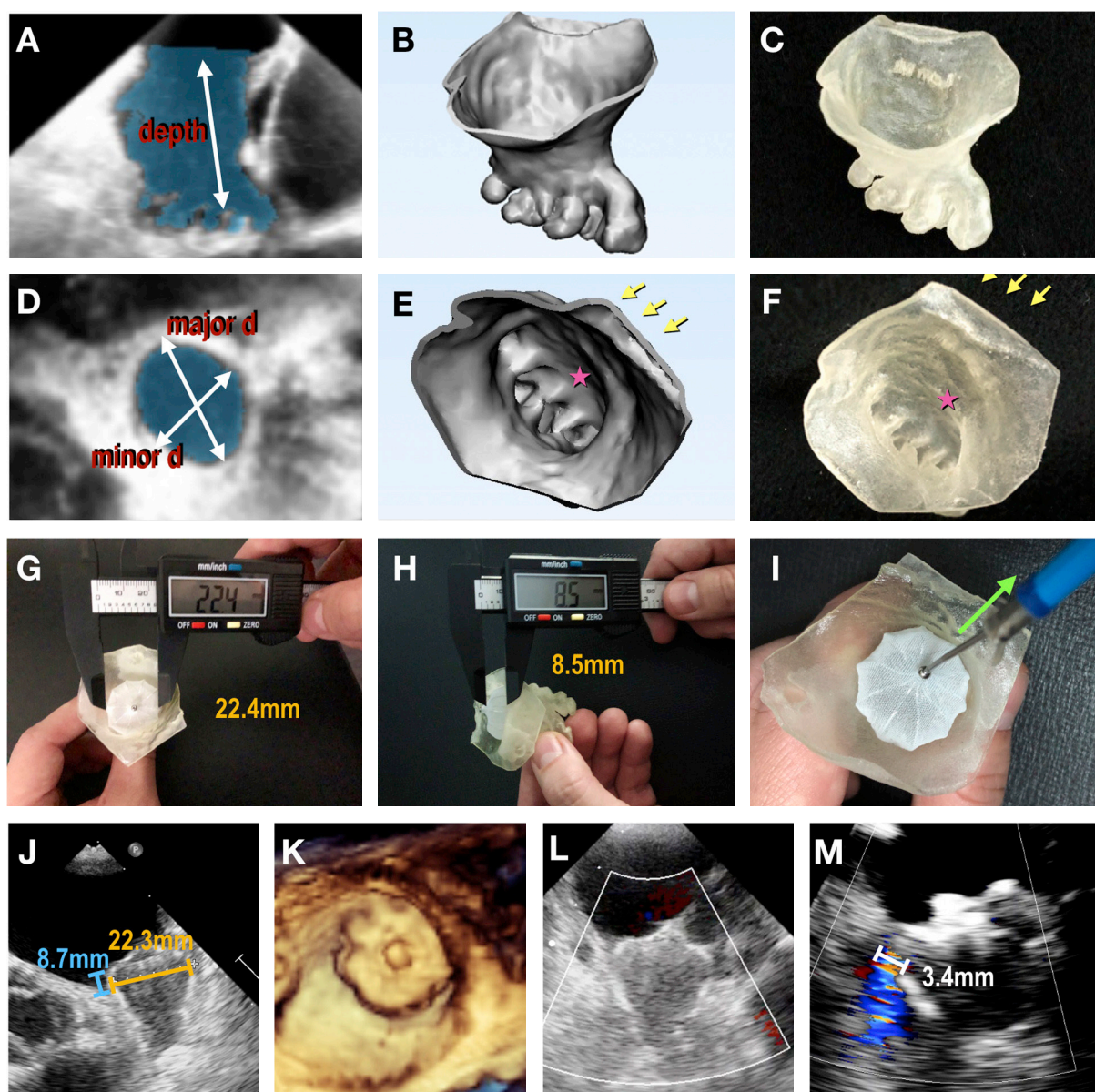


Figure 4. Echocardiography-based 3D printing of patient-specific models. Segmentation of LAA (shaded area) from 3D TEE data (A, D) is turned into a digital object (B, E), and printed using tissue-mimicking material (C, F). The major and minor ostial diameters and depth of the LAA are measured. Arrows denote pulmonary vein ridge; stars denote appendicular trabeculations. Closure devices are then sized and placed within the 3D model (G-I), and device compression and (H) protrusion are measured using a digital caliper. Device stability is assessed using the tug-test (I). Device placement visualized on TEE (J-L), and color Doppler assessment showing no peri-device leak (M). Reprinted with permission from Fan *et al.*^[20]. LAA: left atrial appendage; TEE: trans-esophageal echocardiogram; CT: computed tomography; 3D: three-dimensional

LIMITATIONS

There are numerous limitations to creating and using 3D printed models that have prevented widespread adoption in most programs^[8]. A major consideration is that the creation of 3D models is a time-intensive process requiring familiarity with segmentation and computer automated design software, as well as an in-depth understanding of cardiac morphology^[5]. There is no standardized approach to creating these models, which can ultimately result in a wide variation in the quality of models produced^[7]. This was evidenced by Burkhardt *et al.*^[24] in an article evaluating the inter-operator variability in modeling the RVOT based on the threshold chosen for the initial segmentation. Another limitation is that rigid, or even flexible, 3D

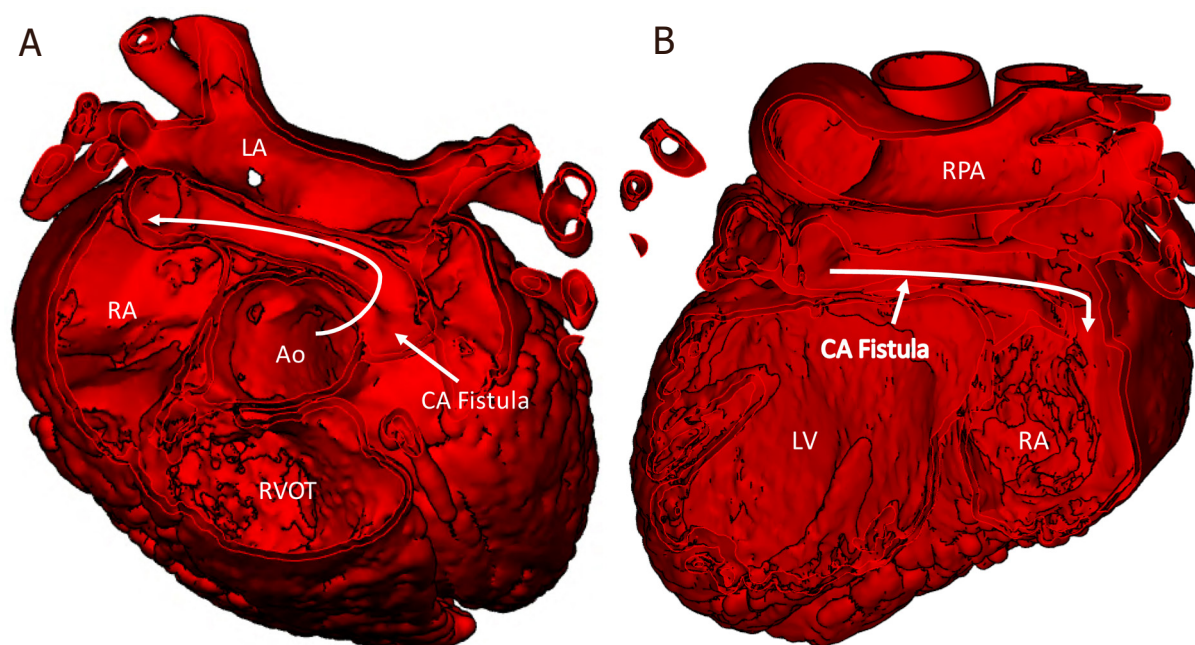


Figure 5. The course of the coronary fistula (CAF) is viewed from a short axis view of the heart. From the leftward aspect of the aortic root, it courses posterior to the aorta (Ao) and rightward to drain into the right atrium (RA) (A); coronal view of the heart, as viewed from the posterior aspect, reveals the course of the CA fistula, almost parallel to the right pulmonary artery (RPA) from left to right to drain into the right atrium (B). CA: coronary artery; LA: left atrium; RVOT: right ventricular outflow tract

printed models only provide a snapshot of the cardiac structure at a specific point in the highly dynamic cardiac cycle, thus limiting our understanding of how these structures will change over the course of one heartbeat. Finally, creation of these models, while helpful in procedural planning, is not reimbursed by most insurance companies, and the prohibitively high cost of the software and 3D printing equipment significantly limits their utility on a routine basis^[1]. More studies are required to further assess the cost-effectiveness and diagnostic accuracy of these models prior to widespread implementation in the field of pediatric cardiology.

FUTURE DIRECTIONS

Recently, there has been movement toward developing materials that more closely mimic the feel and behavior of myocardium, valve leaflets, and vessel walls. Novel materials combined with the use of multiple imaging modalities could also aid in enhanced identification of valve tissue, chordae tendineae, and other structures that are less well defined with current methods. Developing models that accurately mimic both healthy and pathologic tissue would be invaluable in implementing these models routinely^[15]. This advancement would not only allow for more accurate procedural planning but also be invaluable in training surgeons and interventionalists^[2]. Further advances in imaging techniques and software to ease the burden of segmentation would allow for more widespread implementation of this technology to a broader range of conditions. Finally, 3D printing has the potential to aid in the design and construction of patient-specific catheter-based devices for numerous percutaneous interventions, which would further help to decrease procedural complications and improve long-term outcomes.

CONCLUSION

3D printed models have become increasingly invaluable tools in the field of pediatric cardiology. These models improve diagnostic ability, guide perioperative planning, and have thereby ushered in a vast array of new surgical and interventional approaches and techniques. Interventional cardiology has particularly

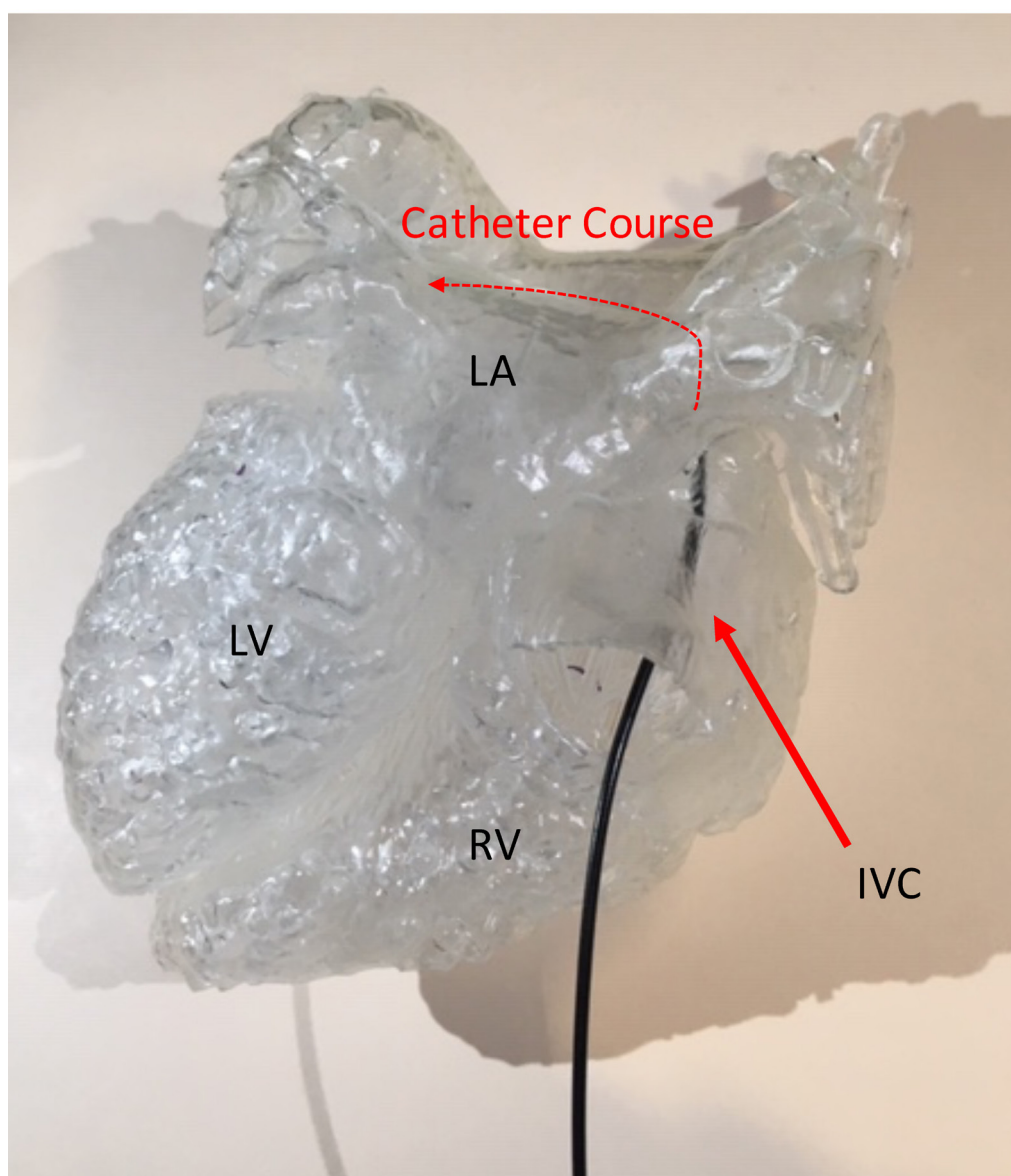


Figure 6. 3D printed model of the CA printed in a clear resin (Formlabs, Somerville, MA) allows planning of the transcatheter approach to closure of the fistula as viewed from the posterior aspect. A catheter courses from the inferior vena cava through the fistula (red dotted line). 3D: three-dimensional; CA: coronary artery; LA: left atrium; LV: left ventricular; RV: right ventricular; IVC: inferior vena cava

benefitted from the advancement of 3D modeling, as the models can be used to devise and adjust procedural approaches and practice percutaneous procedures, which has the potential to drastically reduce complications, decrease procedure times, and significantly limit radiation exposure. Ultimately, the use of 3D models has significantly improved our ability to practice personalized medicine and has helped to enhance the care of patients with cardiac defects through percutaneous procedures.

DECLARATIONS

Authors' contributions

Planning the manuscript content, writing individual sections, proofreading and approval of the final manuscript version: Tredway H, Pasumarti N, Crystal MA, and Farooqi KM

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Intraprocedural guidance in percutaneous mitral valve repair

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Abstract

Percutaneous mitral valve intervention is emerging as a valid alternative for patients affected by mitral regurgitation. By addressing the pathophysiology, therapeutic options mainly target the leaflets, annulus or left ventricle. The present review will cover the intraprocedural guidance of the most used approaches, such as edge to edge repair, adjustable transapical beating-heart chordal implantation and percutaneous direct or indirect annuloplasty. Intraprocedural monitoring relies on integration of fluoroscopy and echocardiography, and is based on the continuous communication between the interventional imager and the interventional cardiologist.

Keywords: Mitral regurgitation, transcatheter mitral valve interventions, percutaneous edge to edge mitral valve repair, percutaneous direct mitral valve annuloplasty, interventional echocardiography

INTRODUCTION

Percutaneous mitral valve intervention is emerging as an alternative for high-risk patients with mitral regurgitation (MR) who are not suitable for conventional open-heart surgery. The current therapeutic options available are classified according to the main physio-pathological targets namely the leaflets, annulus and chordae tendinae.



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The present review will cover the intraprocedural guidance of the most utilised approaches for mitral valve (MV) repair in the setting of MR, such as (1) leaflet repair: edge to edge repair; (2) chordal repair: adjustable transapical beating-heart chordal implantation; and (3) annular repair: percutaneous direct or indirect annuloplasty.

Baseline intraprocedural evaluation of MR grading

MR severity varies in a spectrum, especially in functional MR which is load dependent. Hence, it is imperative to obtain a baseline grading prior to all transcatheter procedures^[1], in order to extrapolate the procedural results under similar hemodynamic conditions and controlled heart rate. In addition, as the ultrasound machine settings (particularly color scale and gain) could influence evaluation, these should be standardized for pre- and post-device evaluation. A multi-modal approach seems the most suitable and appropriate to quantify MR in this setting^[2].

LEAFLET REPAIR: PERCUTANEOUS EDGE-EDGE

The most widely experienced percutaneous approach to MV repair mimics surgical edge to edge repair^[3]. Nowadays two devices are currently available: MitraclipTM system (Abbott Vascular Inc., Menlo, CA, USA) and PASCALTM device (Edwards Life- sciences, Irvine, California).

The crucial procedural steps are the following: (1) safe trans-septal puncture at an optimal site and placement of the guide catheter; (2) steering of the device delivery system (DS) within the LA toward MV plane; (3) perpendicular alignment of DS to the MV coaptation line; (4) creation of the tissue bridge between anterior and posterior leaflet at the target site via grasping and adequate leaflet insertion; (5) evaluation of MR reduction without significant mitral stenosis; and (6) assessment of residual interatrial septal shunt^[4-6].

MitraclipTM system

The MitraclipTM system consists of a polyester fabric covered cobalt-chromium implant with two arms which can be opened and closed with a steerable-guiding mechanism. Currently there are 2 available devices: NTR and XTR.

Intraprocedural monitoring

Under general anesthesia, a trans-septal approach is utilized and the DS is aligned perpendicularly to the MV plane and to the coaptation line of MV leaflets. The device is deployed after successfully grasping of leaflets, at the level of the regurgitant target lesion. In degenerative MR, the clip aims to anchor the flail and/or prolapsing segments, whereas, in cases of functional MR, to improve coaptation of the leaflets. If needed, additional clip(s) may be placed.

Echocardiographic (2D/3D TEE) and fluoroscopic imaging are used during the procedure. Procedural steps and relative imaging modalities are summarized in [Table 1^{\[7\]}](#).

Transseptal puncture

The initial and fundamental step is the trans-septal puncture (TSP) [\[Figure 1\]](#). The determination of the optimal TSP site is of utmost importance for MitraClipTM procedure, as a suboptimal puncture site often leads to additional steering maneuvers to correct the position of the DS within the left atrium (LA), increasing complexity and duration of the procedure. Moreover, optimal puncture height also depends on MV pathology, particularly in cases of degenerative and secondary MR. In patients with prolapse/flail, the puncture site should be higher (~4.5-5 cm above the mitral annulus), thus providing enough space to adequately maneuver the DS within the LA. In cases of secondary MR with prominent apical tethering of the leaflets, since the coaptation point is usually shifted below the annular plane, a lower puncture site

Table 1. Mitraclip™: Imaging modality for each procedural step

Procedural step	Imaging modality		TIPS and TRICKS
	Echocardiography	Fluoroscopy	
1. Tailored Trans-septal puncture	Biplane views: bicaval and SAX views 3D lateral perspective of IAS ME 4-chamber view with retroflexion (height)	AP projection LAO projection	=> sharp tenting should be seen => superior and posterior location in the fossa with a height of 4-4.5 cm to the annulus (see text for details) => avoid PFO
2. Steerable guiding catheter into LA	2D SAX 2D LAX 4-chamber view 3D overhead of LA 3D lateral view	AP projection	=> dilator is removed when the SGC is at least 2 cm across the IAS
3. Clip delivery system into LA	3D overhead of LA 2D ME views	AP projection	
4. Steering and Positioning	Biplane views: commissural and LAX views with and without color Doppler 3D overhead of LA	RAO CRA	
5. Axial alignment	Biplane views: commissural and LAX views	RAO CRA	=> check perpendicularity (3D) and the path of clip (biplane) towards the target lesion
6. Alignment of the Clip arms	3D en face view Biplane views: commissural and LAX views MV SAX transgastric view	RAO CRA	=> clip should be clearly visualized in the LAX view
7. Advancement into LV	Biplane views: commissural and LAX views	RAO CRA	=> re-assess perpendicularity
8. Grasping	Biplane views: commissural and LAX views LAX view (sometimes)	RAO CRA	=> LAX view is of utmost importance => adenosine and breath-hold may be necessary in some cases
9. Assessment of leaflet Insertion	Biplane views from commissure to commissure 2D LAX 2D 4-chamber view SAX transgastric view 3D en face view MPR	RAO CRA	=> multiple two-dimensional views!
10. Procedural Result (pre and post clip deployment)	2D color-Doppler 3D color-Doppler MPR Color-Doppler Pressure gradient MPR valve area	RAO CRA	=> it could be challenging!! REMEMBER: (semi)-quantitative methods (VC and PISA EROA) have not been validated in the presence of split MR jets => pulmonary vein pattern is a good indicator => 3D TEE color Doppler could have a role in quantification => increase in arterial pressure and LV stroke volume may also be helpful indicators => check trans-mitral gradient and residual MV area => careful evaluation of complications (e.g., significant IAS shunt, pericardial effusion)
11. Clip Deployment	Biplane views	RAO CRA	
12. System Removal	Multiple 2D ME views 3D overhead view	RAO CRA	

SAX: short axis; AP: antero-posterior; LAO: left anterior oblique; RAO: right anterior oblique; IAS: interatrial septum; PFO: patent foramen ovalis; LAX: long axis; LA: left atrium; SGC: steerable guide catheter; CRA: cranial; ME: mid esophageal; MV: mitral valve; MPR: multiplanar reconstruction; VC: vena contracta; EROA PISA: effective regurgitant orifice area with proximal isovelocity hemispheric surface area; MR: mitral regurgitation; TEE: transesophageal echocardiography

could be acceptable (~3.5-4.0 cm above the annular plane) as coaptation is dislocated deeper in the left ventricle. Moreover, slight differences in height above the annulus could be determined by the planned positioning of the device in terms of a lateral *vs.* medial regurgitant lesion. A lower TSP site is required for a lateral defect, while higher TSP site is required for a medial defect as a low TSP will move the clip below the mitral annulus when deflecting the system toward the mitral annular plane from lateral to medial.

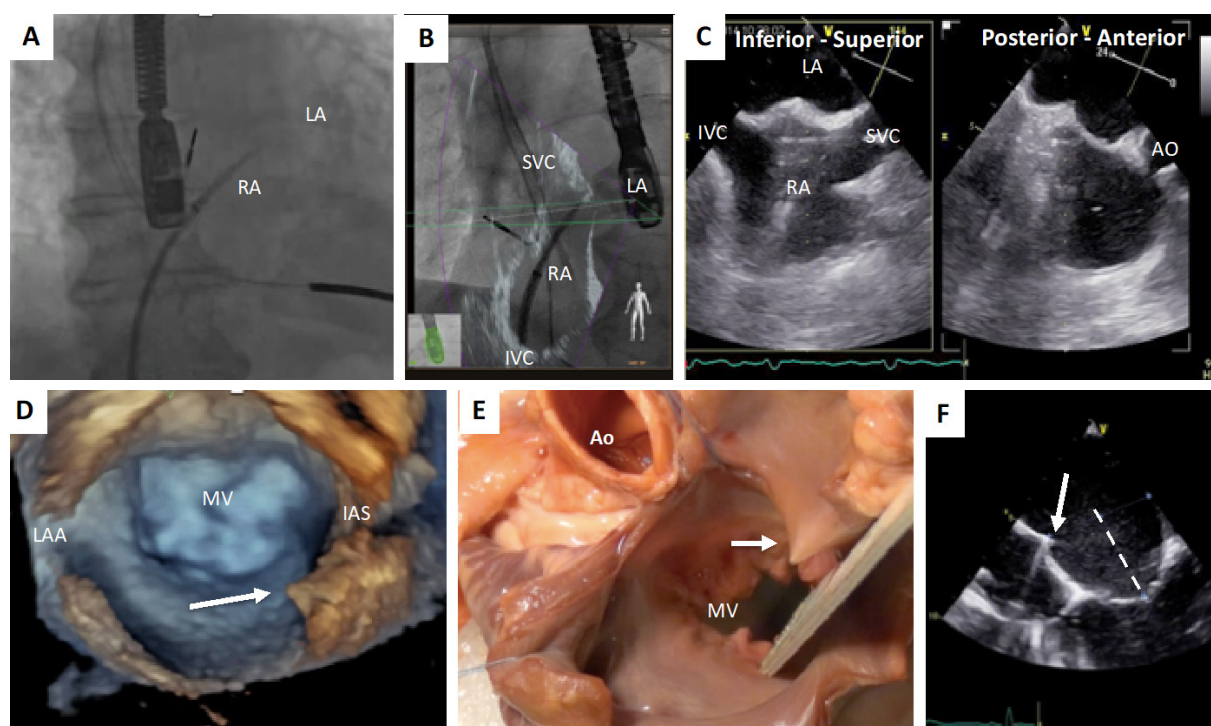


Figure 1. Transseptal puncture. A: AP fluoroscopic projection; B: fusion imaging: LAO fluoroscopic projection with superimposition of the corresponding TEE view (2D bicaval view); C: biplane imaging: the most used views for TSP guidance: bicaval view (left panel) and SAX-B view (right panel). A sharp tenting should be clearly visualized and a superior and posterior localization; D: 3D overhead perspective of the LA clearly highlights the tenting (white arrow); E: TSP simulation on anatomical specimen (pig heart): MV and Ao are clearly visible, while a white arrow highlights the tenting on the left side of the IAS; F: ME 4-chamber view is used to measure the height between the tenting (puncture site, white arrow) and the annular plane. AP: antero-posterior; RA: right atrium; LA: left atrium; IVC: inferior vena cava; SVC: superior vena cava; Ao: aortic root/valve; MV: mitral valve; IAS: interatrial septum; LAA: left atrial appendage; LAO: left anterior oblique; TEE: transesophageal echocardiography; TSP: trans-septal puncture; SAX: short axis

With atrial dilation which is common in MR patients, the location/angle of the interatrial septum (IAS) in relation to the MV plane may be distorted. This distortion is difficult to appreciate on 2D imaging; thus, 3D TEE confirmation of TSP location is recommended in such cases. Access via a patent foramen ovalis is not recommended, although the entry site into the LA would be superior as the defect is generally too anterior and the tunnel constrains the trajectory of the steerable guide catheter (SGC) tangent to the IAS and toward aortic root. Access via an atrial septal defect (ASD) is also not recommended for two main reasons: (1) the size of the defect generally does not match the size of the SGC; and (2) in most cases the septum does not provide proper support for a stable position of the SGC and there is an increased risk of septal rupture.

Steerable guide catheter insertion into left atrium

Crossing of the IAS should be visualized in the 2D SAX-B view or intermediate view between SAX and bicaval views or by several 3D perspective of LA. Both views allow visualization of the distal portion of the transseptal needle and its passage into the LA [Figure 2]. The insertion of the SGC should be carefully monitored by 2D (mid-esophageal short-axis, long-axis, and four-chamber views are recommended), 3D overhead perspective of LA and fluoroscopic imaging, in order to avoid injuries of the LA wall. Persistence of tenting denotes that the SGC has still not completely crossed the septum.

The dilator should be removed when the SGC is at least 2 cm across the IAS. Fluoroscopy and echocardiography both help in differentiating the dilator from the SGC.

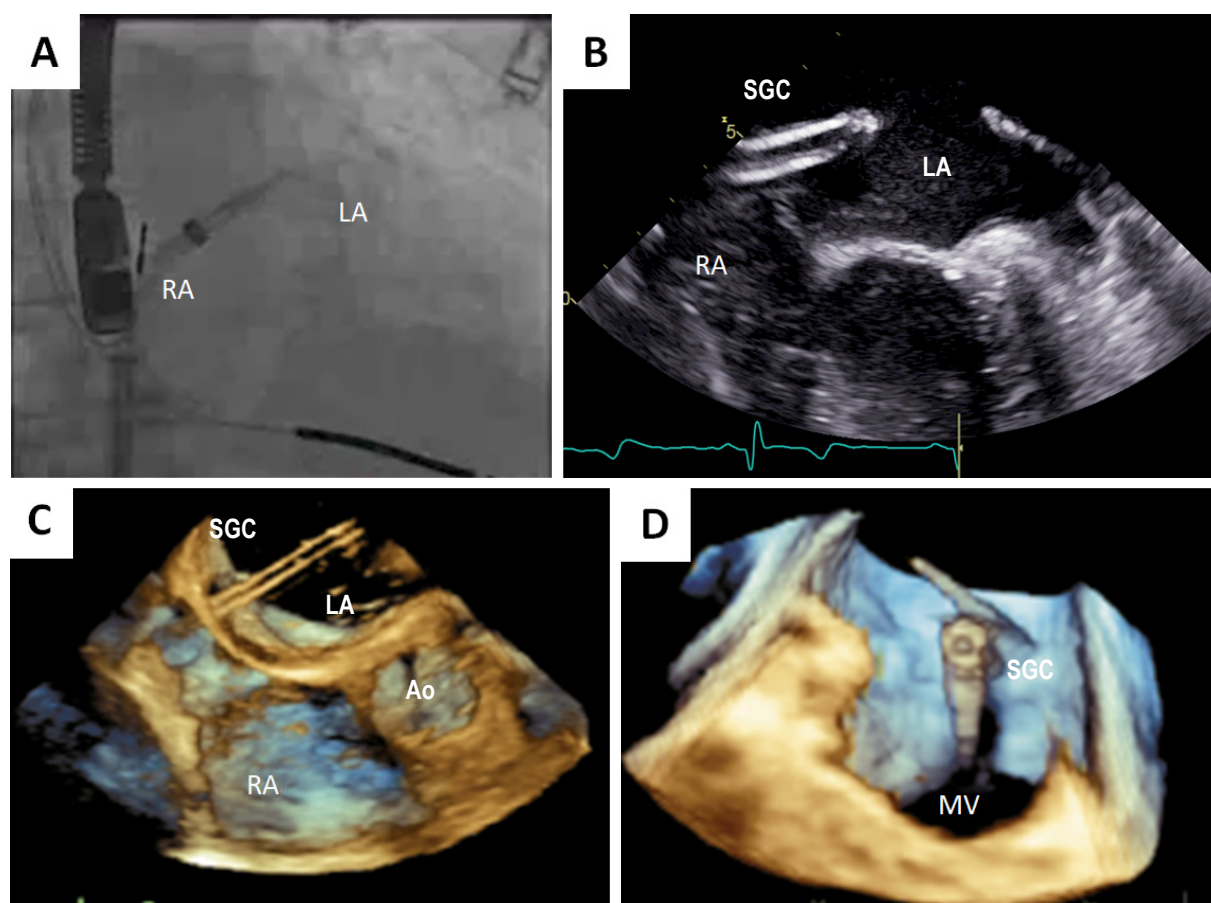


Figure 2. Steerable guide catheter insertion into left atrium. A: AP fluoroscopic projection showing both transseptal sheath and dilator inside the LA; B-D: SGC trough the septum inside the LA after removing the dilator: the dilator can be identified by its typical echogenic coils striations at the cone tip, whereas the tip of the SGC is marked with a radiopaque echo bright rail-road shaped artifact and can be identified by 2D TEE (B) and 3D TEE (C: lateral perspective; D: en face perspective). SGC: steerable guide catheter; RA: right atrium; LA: left atrium; Ao: aortic root/valve; MV: mitral valve

Clip delivery system advancement through the catheter into left atrium

The clip delivery system (CDS) is then gently advanced into the LA through the SGC under fluoroscopic and TEE guidance [Figure 3]. The 3D TEE overhead perspective of the LA offers the best comprehensive view of spatial relationships among structures and device, as gross DS movements in the center of the LA are required. When the DS is directly adjacent to the lateral atrial wall, 2D imaging (short axis and 4 chamber views, or simultaneous multiplane view) is more useful thanks to the better spatial resolution for evaluating the relationship between the Clip and LA structures and it is the preferred imaging modality for guiding the steering toward MV plane. At this stage, the 2D TEE view (usually in between short axis and bicaval views) is also useful to confirm the position of SGC across the IAS inside the LA.

Steering and positioning the clip in the left atrium

The DS is steered towards the MV over the target lesion (the tip of the clip should point towards the largest color flow convergence zone and should split the regurgitant jet) [Figure 4]. A series of steering maneuvers in anterior-posterior and/or medial-lateral directions allow the achievement of the desired position over the MV target lesion. This step is usually monitored by 3D overhead perspective of the LA for gross DS movement and 2D simultaneous biplane views for fine adjustments: a mid-esophageal commissural view ($\sim 60^\circ$) to perform medial-lateral adjustments and a long-axis view at 120° - 150° (LAX view) to monitor anterior-posterior adjustments.

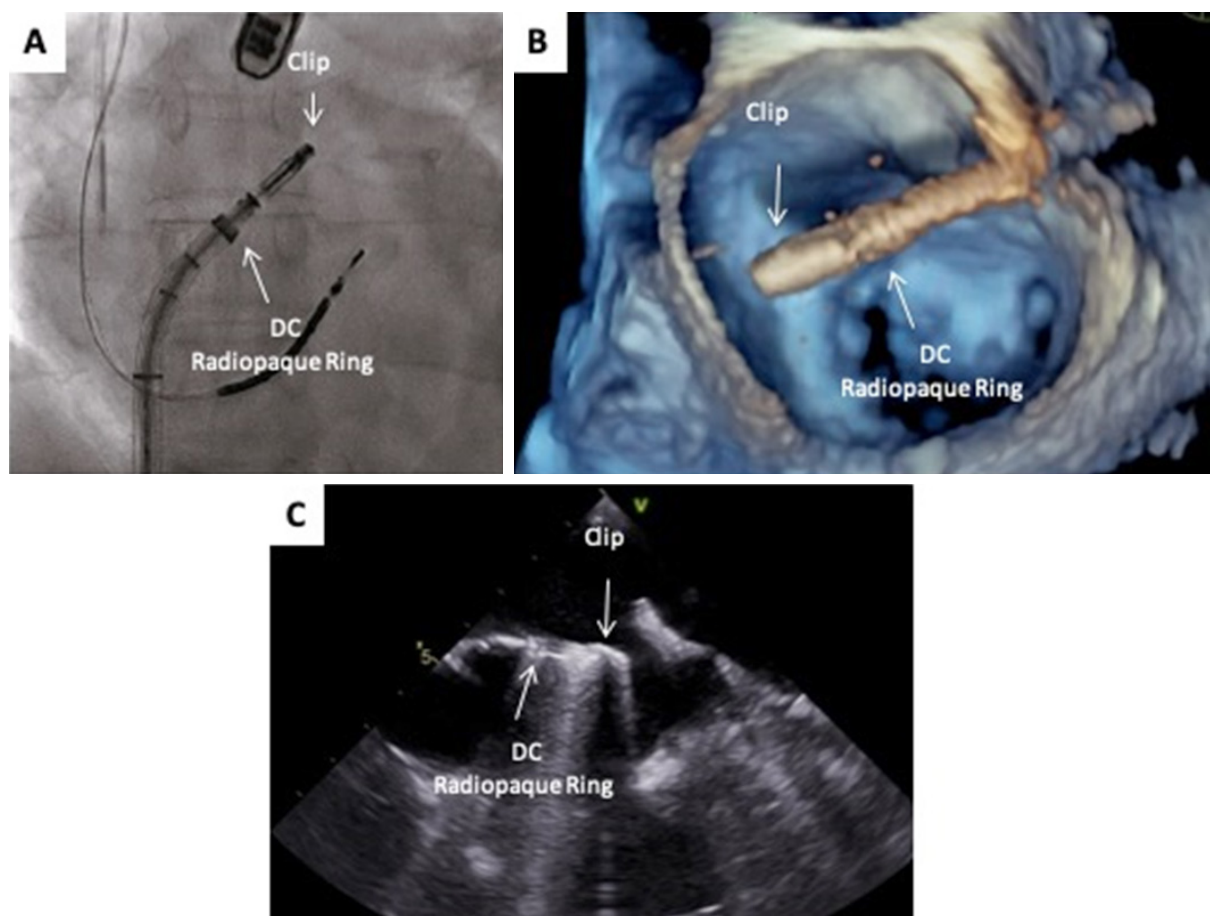


Figure 3. Clip delivery system advancement through the catheter into left atrium. The clip delivering system inside LA imaged with different modalities, A: AP fluoroscopic view; B: 3D overhead perspective of the LA; C: 2D mid-esophageal 4 chamber view. DC: clip delivery catheter; AP: antero-posterior; LA: left atrium

Axial alignment of the clip delivery system

The proper trajectory should ensure perpendicularity of the device in relation to the MV plane, avoiding a slanting one. Misalignment can lead to incorrect advancement of DS into LV, affecting both symmetry and efficacy of the grasping (e.g., difficult or insufficient grasping of one of the leaflets, distortion of the coaptation line). This aspect is of utmost importance in cases of commissural lesions to avoid chordal entrapment. Fluoroscopy, echocardiography and fusion imaging guidance are useful for this procedural step [Figure 5].

Alignment of the clip arms to the coaptation line

Once the appropriate axial alignment of the DS is achieved over the target lesion, the arms of the Clip can be deployed. The Clip arms should be oriented perpendicularly to the coaptation line. Clip orientation is monitored by 3D TEE en face view of the MV together with 2D simultaneous biplane views [Figure 6]. In the case of central Clip location, if proper position is achieved, no Clip arms should be seen in the commissural view and both clip arms should be visualized in full length in the LAX view. Additionally, in the RAO cranial fluoroscopic projection, clip arms should not be visible. Instead, if the Clip is positioned in the lateral or medial region of the valve, Clip arms can be partially visible in the commissural view. In this last case, the LVOT view can be useful for assessment of fully opened Clip arms. Additionally, short-axis transgastric view can be used to confirm perpendicularity of Clip arms to the coaptation line.

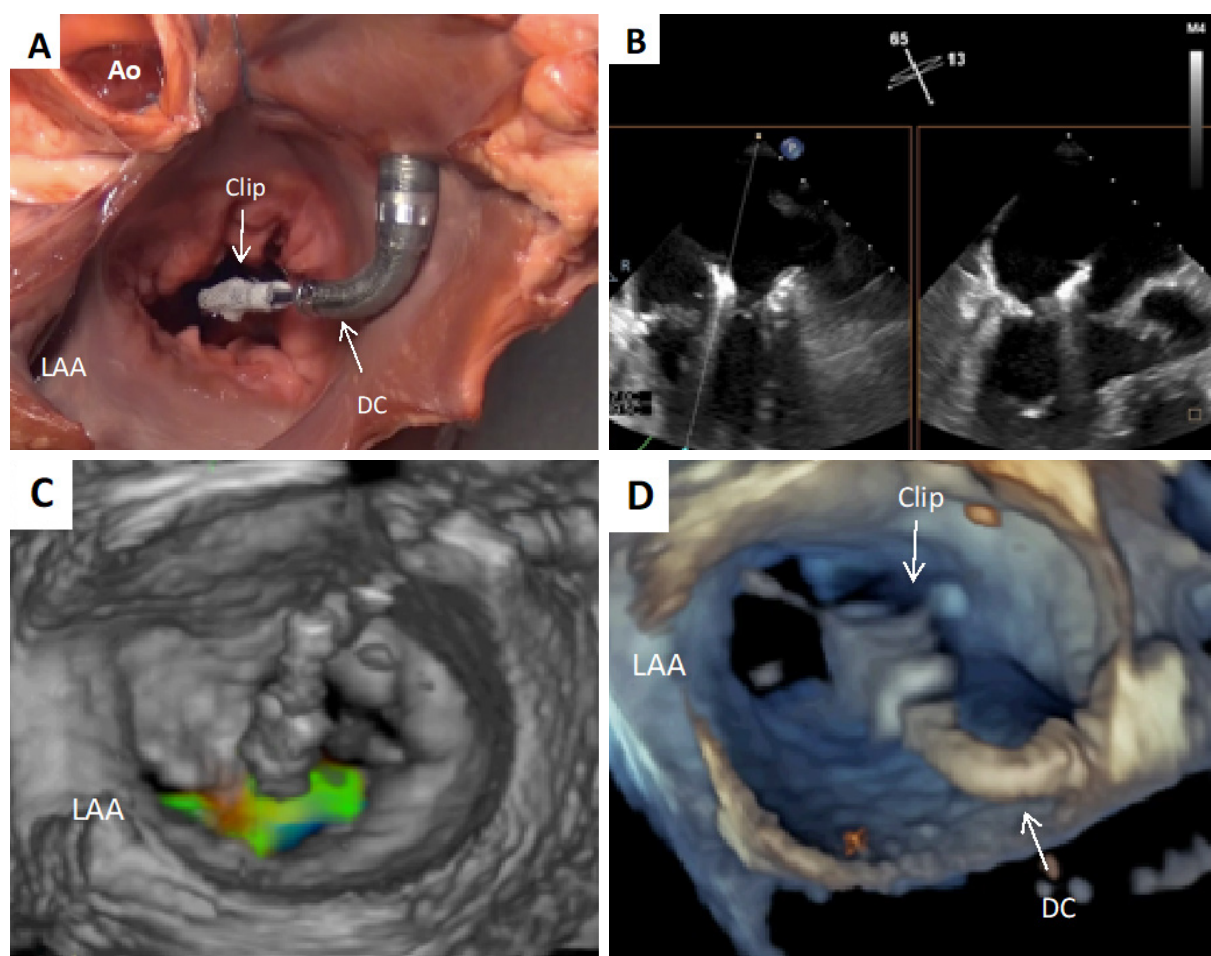


Figure 4. Steering and positioning the clip in the left atrium. A: anatomical specimen (pig heart) showing the steering of the clip towards the MV: reference landmarks are LAA and Ao; B: biplane imaging guiding the steering towards the MV: commissural view for medio-lateral and LAX view for postero-anterior guidance; C, D: 3D overhead perspective of the LA with (C) and without (D) color guiding the steering and the positioning of the device. DC: Clip delivery catheter; LAA: left atrial appendage; LA: left atrium; Ao: aortic root/valve; MV: mitral valve; LAX: long axis

Advancement into left ventricle

The DS is then advanced distally across the MV, with Clip arms partially closed (60°), approximately 2 cm below the MV into the LV under fluoroscopic and TEE guidance. This step is monitored by 2D simultaneous biplane views (commissural and LAX views) [Figure 7]. Once the clip is below the MV plane, and the arms are fully opened, correct positioning should be verified by the visualization of mitral leaflets moving freely above Clip arms and splitting of the MR jet. In order to preserve perpendicularity with the coaptation line, it is important to reconfirm the correct Clip orientation under simultaneous biplane views and 3D en face view, as the Clip may rotate during the passage across the MV. Using the 3D en face view, it is possible to progressively reduce the gain until the MV leaflets become almost transparent, allowing visualization of the Clip arms proper orientation, or alternatively using the simultaneous 3D display from LA and LV. Inside the LV, changes in Clip arms orientation should be minimal to avoid entanglement in the chordae tendinae. In case of significant orientation adjustment (> 90° in each direction), the Clip should be everted and withdrawn back into the LA where its orientation may be safely manipulated, avoiding chordae entanglement that may make difficult or even impossible to remove the Clip or even damage MV.

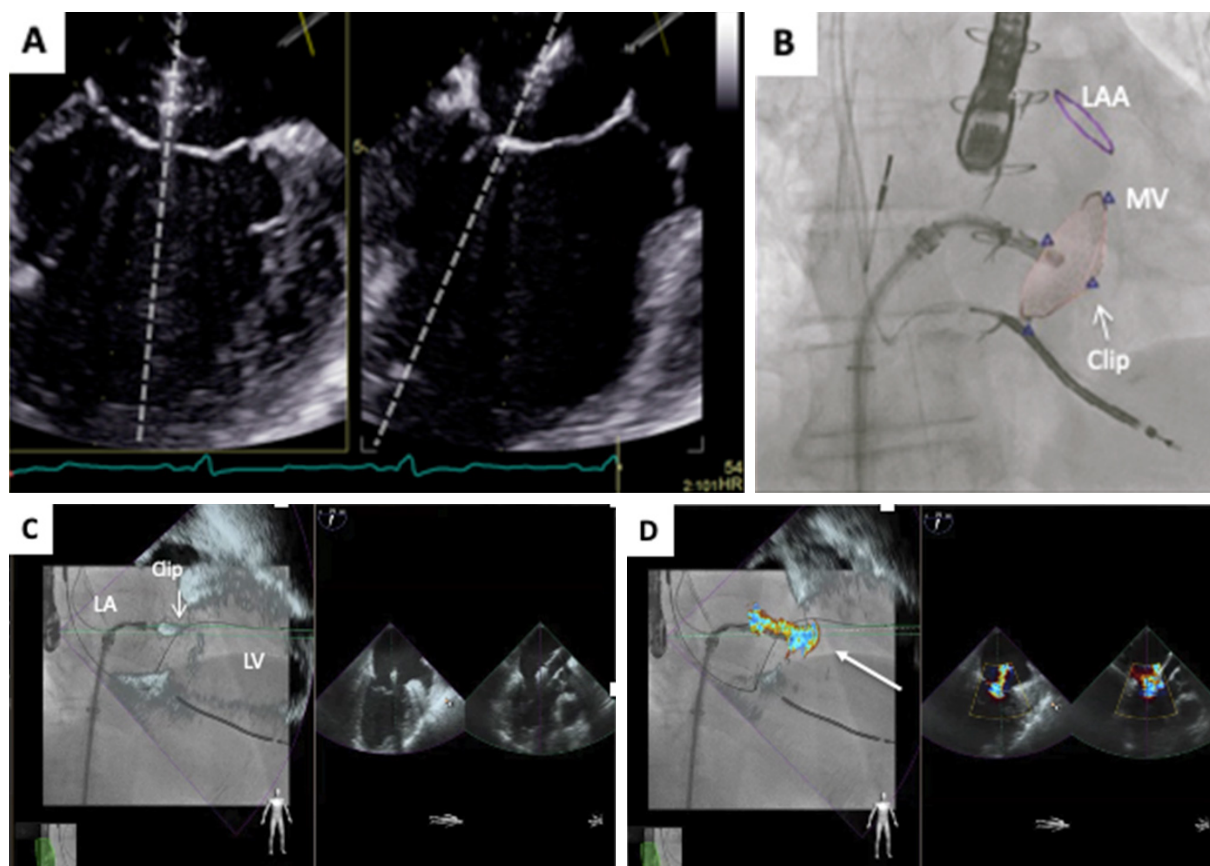


Figure 5. Axial alignment of the clip delivery system. A: biplane imaging, starting from the commissural view as the main view and the LAX view as the derived one, allows for medial-lateral and anterior-posterior clip adjustments. The perpendicularity of the system with respect to the MV plane should be achieved in both views; B-D: fusion imaging showing the same procedural step: RAO CRA fluoroscopic projection with superimposed commissural view with (D) and without (C) color. LAA: left atrial appendage; LV: left ventricle; LA: left atrium; MV: mitral valve

Leaflets grasping

Once the Mitraclip™ is in the proper position in the left ventricle, it is useful to recheck its orientation; in addition, 3D lateral perspective of the left atrium and ventricle could be useful to evaluate the angle of the clip before full grasping.

Subsequently, leaflet grasping is performed by slowly retracting the system back towards the LA, to allow the leaflets to come to rest on the Clip arms. Once both leaflets are visualized over the Clip arms with tips ideally adjacent to the shaft, the grippers are lowered onto the leaflets. This step is usually monitored by a 2D simultaneous biplane view, focused on LAX view, in addition to fluoroscopy [Figure 8]. In cases of para-commissural Clip placement, simultaneous biplane view starting from the commissural view as a reference plane may not provide adequate visualization of equal Clip arm lengths together with the anterior and posterior leaflets on the derived LAX view (due to inadequate angulation of the elevation plane). It could be useful to transiently refer to the 2D LAX view which provides more adequate visualization of equal Clip arm full lengths.

It is important to continuously visualize leaflet insertion while grasping to avoid rolling leaflets/chordae. Partial closure of the Clip until the arms angle is ~60° is recommended, and this distinct “V” shape should be maintained on fluoroscopy. When the Clip appears properly positioned, leaflet insertion and MR reduction appear satisfactory without inducing stenosis, the Clip can be fully closed.

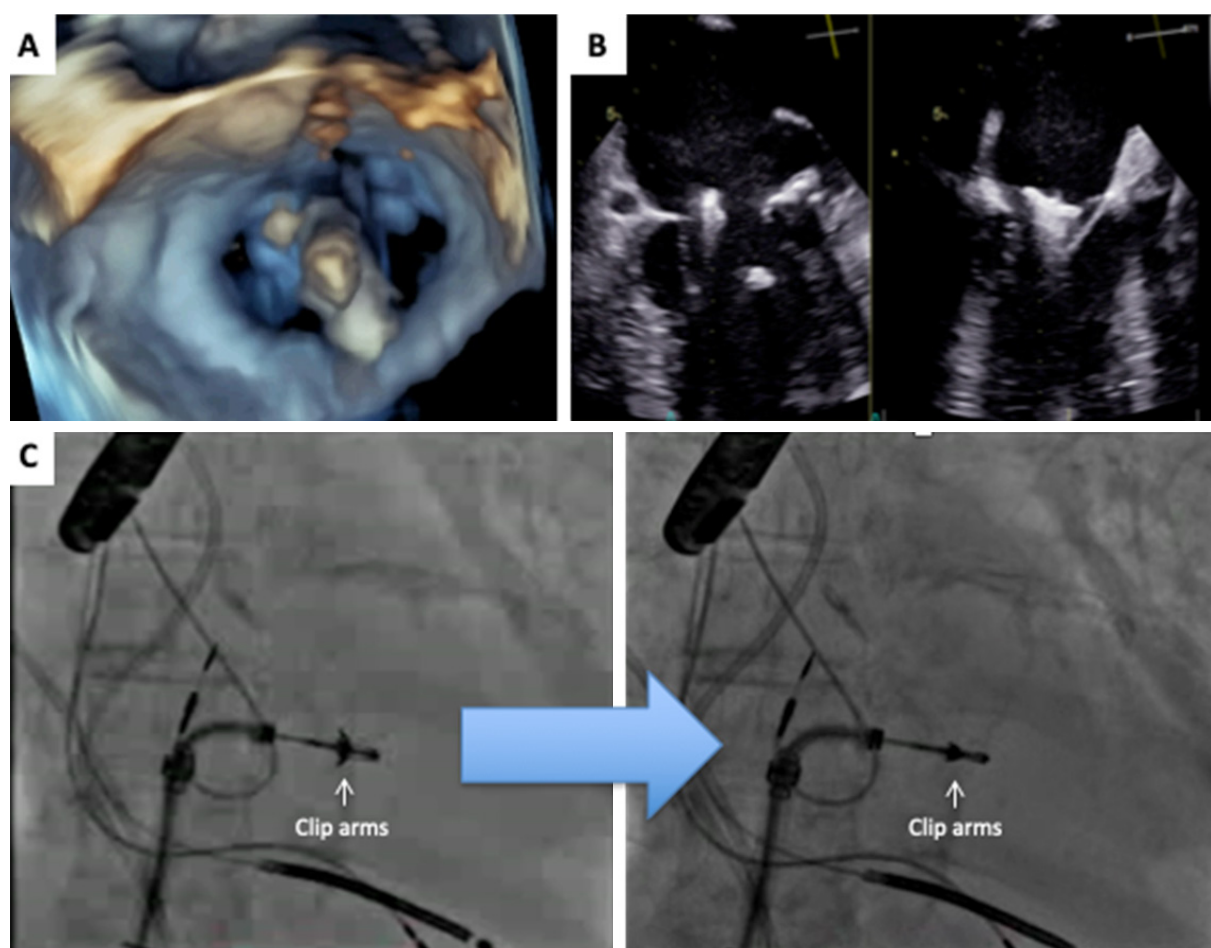


Figure 6. Alignment of the clip arms to the coaptation line. A: 3D MV en-face view guiding clip arms orientation with respect to the coaptation line; B: biplane imaging: clip arms should be visible only in LAX view; C: RAO CRA fluoroscopic view: after adequate rotation according to the echo guidance, clip arms are not visible anymore (right panel). LAX: long axis view; RAO CRA: right anterior oblique cranial projection; MV: mitral valve

Assessment of leaflet insertion

The acquisition of a long loop is helpful as the grasping can be re-evaluated whenever needed. Adequate leaflet insertion is verified when direct and indirect signs are simultaneously present. Direct signs [Figure 9]:

- (1) The length of the leaflet captured inside the Clip should be ≥ 5 mm (some have reported at least 4 mm), with both leaflets inserted into the atrial aspect of the closed Clip arms (the length of leaflet captured inside the Clip is determined by subtracting the leaflet length outside the Clip from the corresponding leaflet length at baseline);
- (2) The leaflet draped over the closed arms should have a reduced mobility relative to the tips of the Clip arms. Leaflets motility can be easily assessed by the 2D simultaneous biplane view, using the commissural view as the main view and moving the elevation plane along the MV from the posterior-medial orifice to the anterior-lateral one, closely to the edge of the Clip. The quality of insertion of the posterior and anterior leaflets is usually best evaluated in LAX and 4-chamber view respectively;
- (3) The occurrence of a double MV orifice: the 3D en face view of MV from LA or LV perspectives as well as the 2D short axis transgastric view of MV are helpful to assess the new geometry of the valve and should show a double-orifice valve with an adequate tissue bridge over the Clip arms. In addition, multiplanar reconstruction of the same 3D dataset allows for further evaluation of the leaflets.

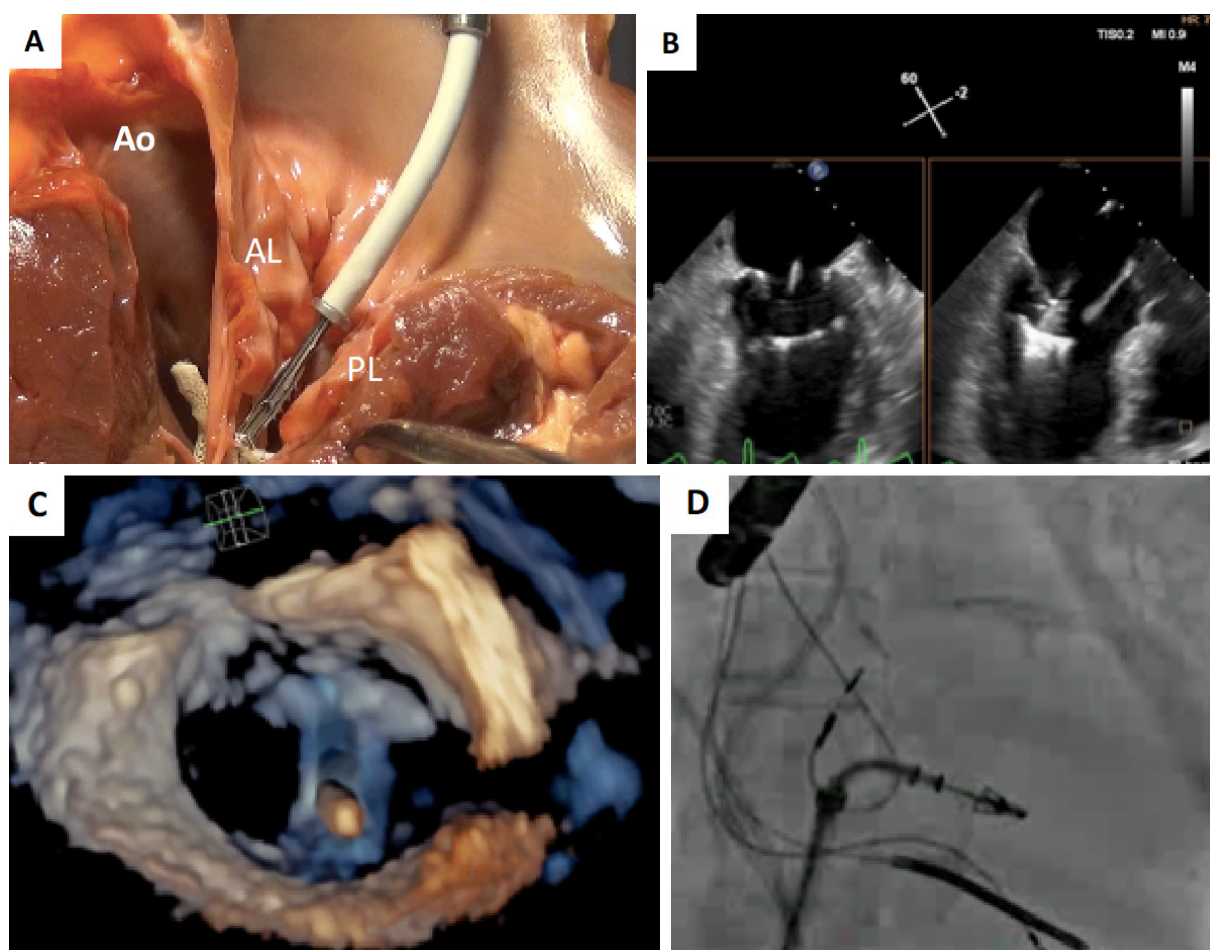


Figure 7. Advancement into LV. A: anatomical specimen (pig heart) showing clip advancement into LV: lateral perspective of the clip advanced into the left ventricle; B: Bi-plane imaging showing clip advancement into left ventricle; C: 3D MV en face view after reducing the gains shows clip arms and their orientation across MV; D: RAO fluoroscopic view shows clip inside LV across the MV. Ao: aortic valve/root; AL: anterior leaflet; PL: posterior leaflet; RAO: right anterior oblique; LV: left ventricle; MV: mitral valve

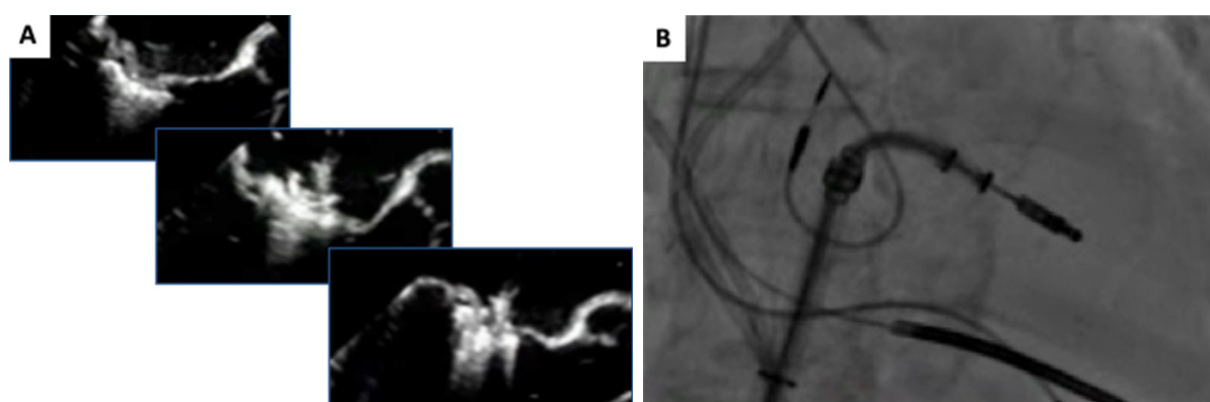


Figure 8. Leaflets Grasping. A: sequential zoomed LAX view of leaflets grasping; B: RAO fluoroscopic projection showing clip with closed arms. LAX: long axis view; RAO: right anterior oblique

Indirect signs of adequate leaflets grasping are [Figure 10]: the presence of MR reduction, the absence of intraclip jet (that may suggest inadequate amount of leaflet tissue grasped into Clip arms), the appearance of spontaneous echo contrast in LA/LAA.

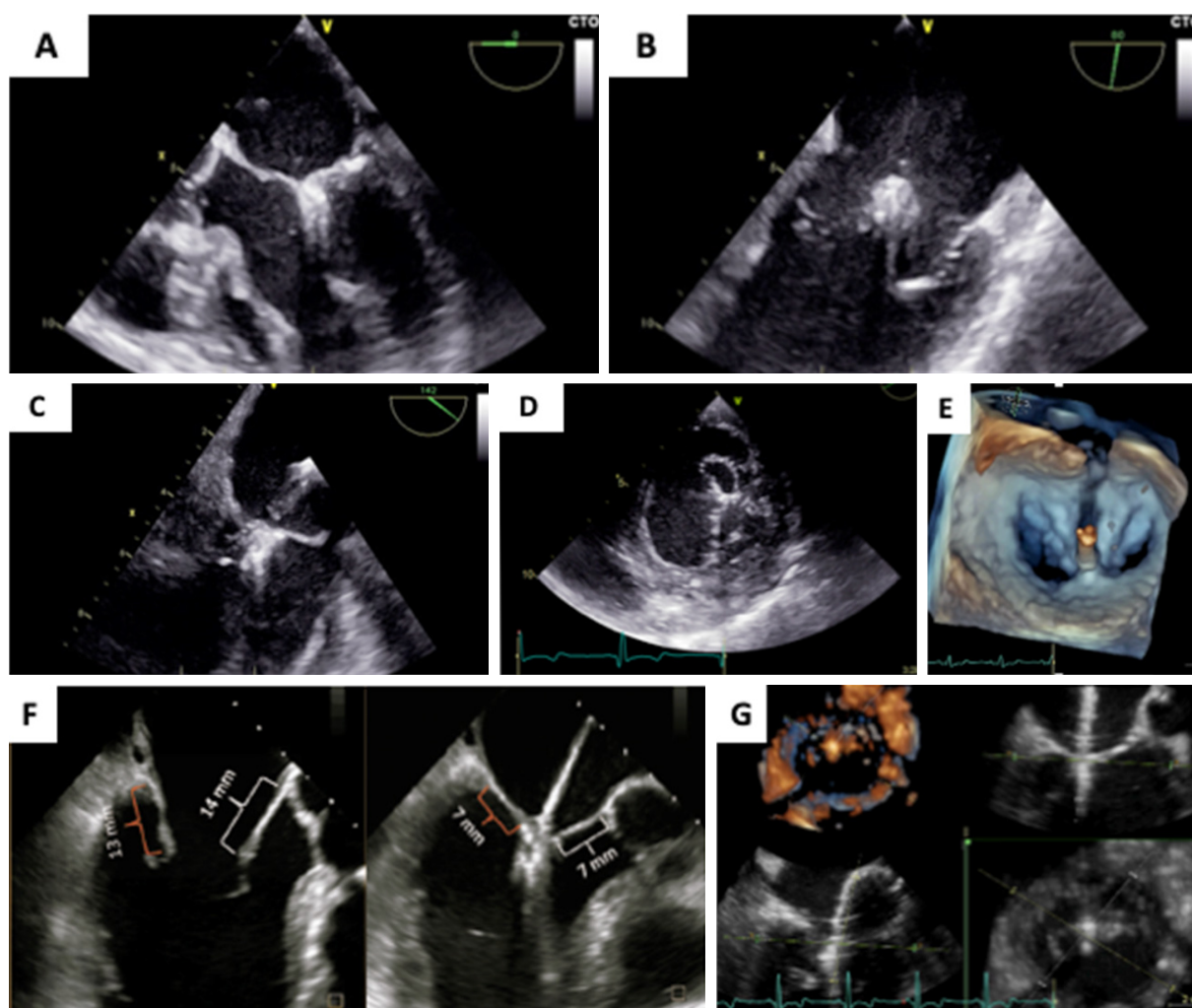


Figure 9. Assessment of leaflets insertion. Verification of satisfactory grasp of the leaflets requires multiple views: 4-chamber view (A), commissural view (B), long axis view (C), transgastric short axis view (D), 3D en face view (E); measurement of leaflets length before and after grasping (F); multiplanar reconstruction allows simultaneous visualization of different views (G)

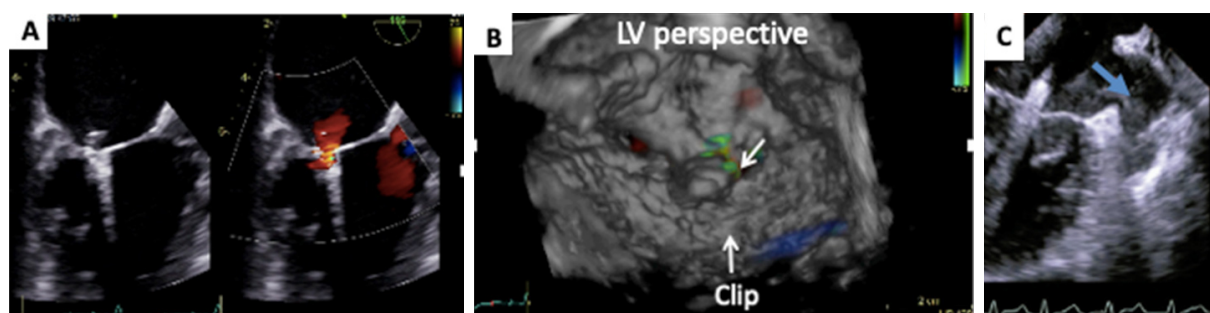


Figure 10. Assessment of Leaflets Insertion: Indirect Signs. 2D color Doppler (A) and 3D LV perspective (B) showing a residual intraclip jet; appearance of spontaneous echocontrast after leaflet grasping (C). LV: left ventricle

Assessment of result before Clip release

The best result should be a proper balance between tolerable transmitral pressure gradient (TMPG) and adequate reduction of MR.

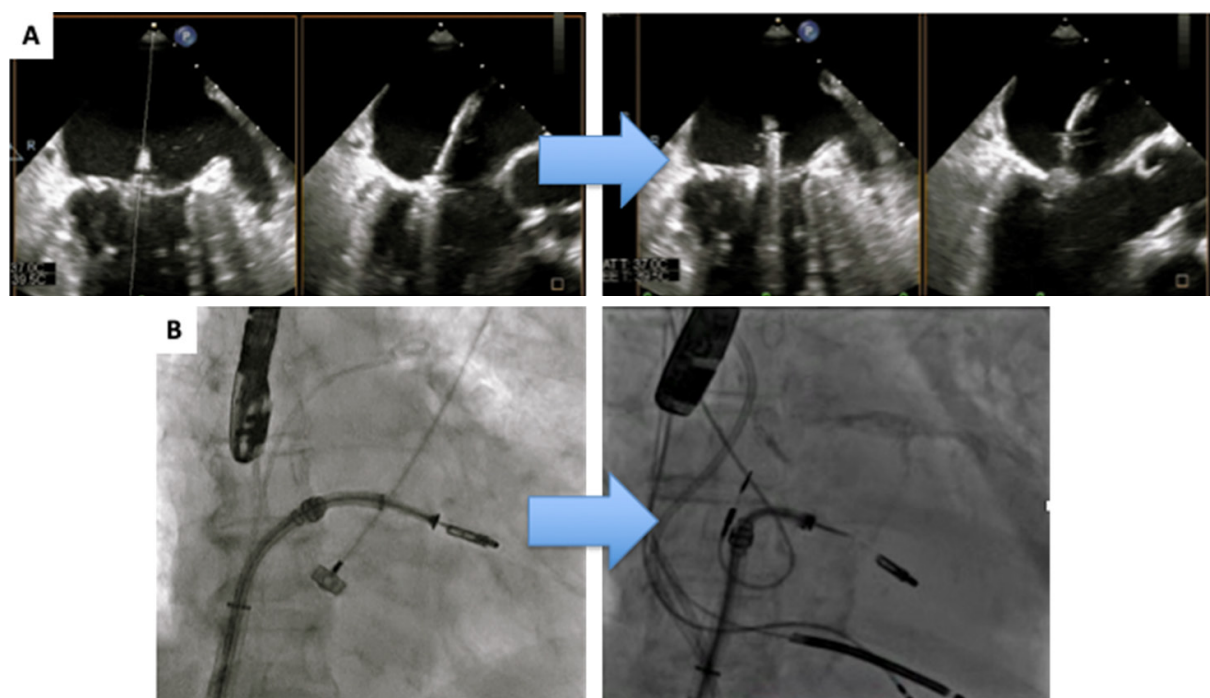


Figure 11. Clip release. Biplane imaging (A) and right anterior oblique fluoroscopic projections (B) showing clip release

The risk of mitral stenosis has to be evaluated by the assessment of diastolic TMPG via continuous-wave (CW) Doppler after the placement of each Clip.

Planimetric assessment of the MV area provides an additive information. It should be preferably assessed by using 3D imaging, which allows for multiplanar reconstruction^[8]. Alternatively, 2D planimetry could be performed in the mid-diastole phase using the transgastric short-axis view. In both cases, the edges of the MV leaflets should be clearly visible, allowing the inner edge of each orifice to be traced and the areas added to calculate the total size of the newly formed orifices.

By combining both information, TMPG and MVA, it is possible to estimate the risk of iatrogenic mitral stenosis more accurately. An $MVA \leq 1.5 \text{ cm}^2$ and a $TMPG \geq 5 \text{ mmHg}$ were considered criteria to indicate significant MS in the EVEREST studies^[9,10].

Moreover, intraprocedural TMPG measured by TEE under general anesthesia conditions potentially underestimates the hemodynamic impact of reduced MVA in daily life with exercise, which operators should be aware of when deciding on implanting one or more clips^[10].

Together with MVA and TMPG, the assessment of the final geometry of the MV should ensure: (1) each clip is placed symmetrically on both leaflets and that the Clip is not biased towards one of them; and (2) excessive distortion of the leaflets is avoided as it may lead to unbalanced traction and potentially cause partial Clip detachment or leaflet rupture during follow-up. 3D en face view with atrial or ventricular perspective is a fundamental imaging tool for this evaluation.

Clip release

Once the Clip position is appropriate and MR effectively reduced, the Clip is detached from the catheter shaft usually under 2D imaging and fluoroscopic guidance [Figure 11]. A stable Clip position has to be reconfirmed and the grade of residual MR should be reassessed by Color Doppler, as minor changes can occur when the tension transferred via the DS disappears.

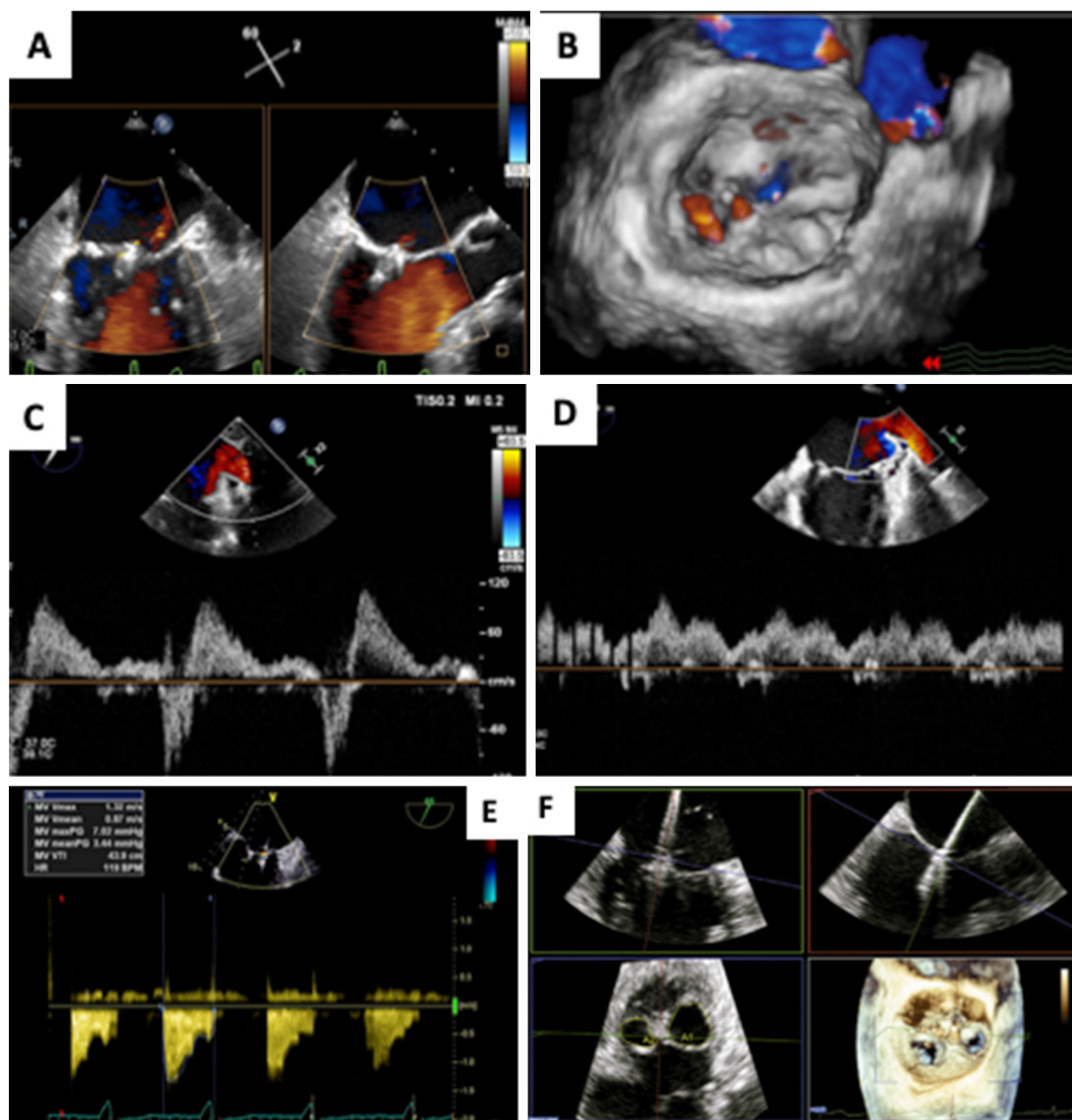


Figure 12. Assessment of result after clip release. A: biplane imaging and 3D en face (B) with color Doppler showing a residual jet from the lateral orifice; C: baseline evaluation: systolic flow reversal at Pulse Wave Doppler interrogation of the LSPV; E: post-procedural evaluation: normalization of systolic flow in the LSPV; F: evaluation of the transmitral pressure gradient; G: Multiplanar reconstruction: evaluation of residual mitral valve area. LSPV: left superior pulmonary vein

Assessment of result after Clip release

Similar hemodynamic conditions and the same ultrasound settings are required to make a valuable comparison between baseline and post-Clip MR. In particular, blood pressure needs to be normalized.

A multi-modal approach provides the most suitable and appropriate method to characterize and quantify residual MR^[11] [Figure 12]:

(1) Color-Doppler is the main initial modality for MR assessment, in terms of site, number of jets, eccentricity, vena contracta, and flow convergence, throughout the whole procedure, allowing rapid and easy evaluation of MR. PISA method is less reliable and therefore not recommended for flow quantitation and EROA calculation;

- (2) The 3D color-Doppler vena contracta area (VCA) seems promising as it is able to overcome the limits and the assumption of EROA-PISA evaluation^[12,13]. Indeed, each jet that is deemed significant would need to be separately analyzed for VCA, since they are often in different planes and with different orientations, and their VCAs can be added. It must be remembered that 3D color Doppler could be limited by a low frame rate. Furthermore, 3D color can help identify, assess, and localize residual eccentric or wall-hugging MR jets not seen on 2D color flow imaging. However, to date there is no sufficient data to routinely recommend 3D VCA as a strong parameter to quantify residual MR after clip placement;
- (3) The pulmonary vein flow pattern is very useful to assess residual MR grading. Normalization of pulmonary vein flow after MV interventions strongly suggests that MR has been reduced to mild;
- (4) Invasive hemodynamic parameters, such as the resolution of regurgitant atrial v wave and reduction of left atrial or pulmonary pressures, provide important additional clues to improvement in MR severity. It is also common to observe an increase in systolic blood pressure immediately after a successful reduction in severe MR, reflecting an increase in forward stroke volume;
- (5) The mitral inflow velocity pattern (decrease in mitral E velocity and velocity time integral) may be helpful in assessing reduction of MR, as a change from an E-wave-dominant to an A-wave dominant pattern could suggest mild residual MR. A diastolic TMPG rise, without significant reduction of MVA could be an indirect sign of residual moderate or greater MR. In such a setting, an additional Clip may “paradoxically” reduce the diastolic TMPG by the improvement of MR;
- (6) Appearance of spontaneous echocontrast in the LA after MV repair also suggests significant reduction in MR severity;
- (7) Left ventricular outflow tract velocity integral as assessed in deep transgastric views may be helpful in demonstrating an increase in forward systemic flow;
- (8) A decline in LV ejection fraction after MitraClipTM procedure also could suggest significant MR reduction and thus increased afterload.

System removal

After release of the Clip, the CDS is withdrawn into SGC. The distal end of the DS, also called the atraumatic tip, may injure LA structures during withdrawal into the SGC. This maneuver is usually monitored by multiple views in 2D imaging. At this stage, an intermediary between short axis and bicaval views, is also useful to confirm that the SGC is maintained sufficiently into the LA, as a second Clip implantation may be required. If no additional Clip is needed, the SGC is withdrawn back across the IAS and out of the femoral vein access.

Atrial septal defect evaluation

After system removal, the residual shunt and size of iatrogenic IAS shunt should be evaluated. Assuming no additional damage to the septum and predominantly left to right flow, the defect is generally of no clinical significance^[14].

Complications

Percutaneous edge to edge MV repair is generally a safe procedure with good hemodynamic tolerance even in high-risk patients and is associated with few major complications^[15,16]. Serious complications may occur at a low rate and can be promptly identified by echocardiographic monitoring during the procedure. Potential complications may be represented by:

- (1) The occurrence of thrombus on intracardiac devices, such as guidewires and/or delivery sheaths;
- (2) Acute severe hypotension caused by cardiac tamponade, acute decline of LV function, or worsening of MR;
- (3) Pericardial effusion and cardiac tamponade due to perforation of the LV free wall or aortic puncture during TSP;
- (4) MR worsening, subtended by three major mechanisms: leaflet or chordal damage; loss of leaflet

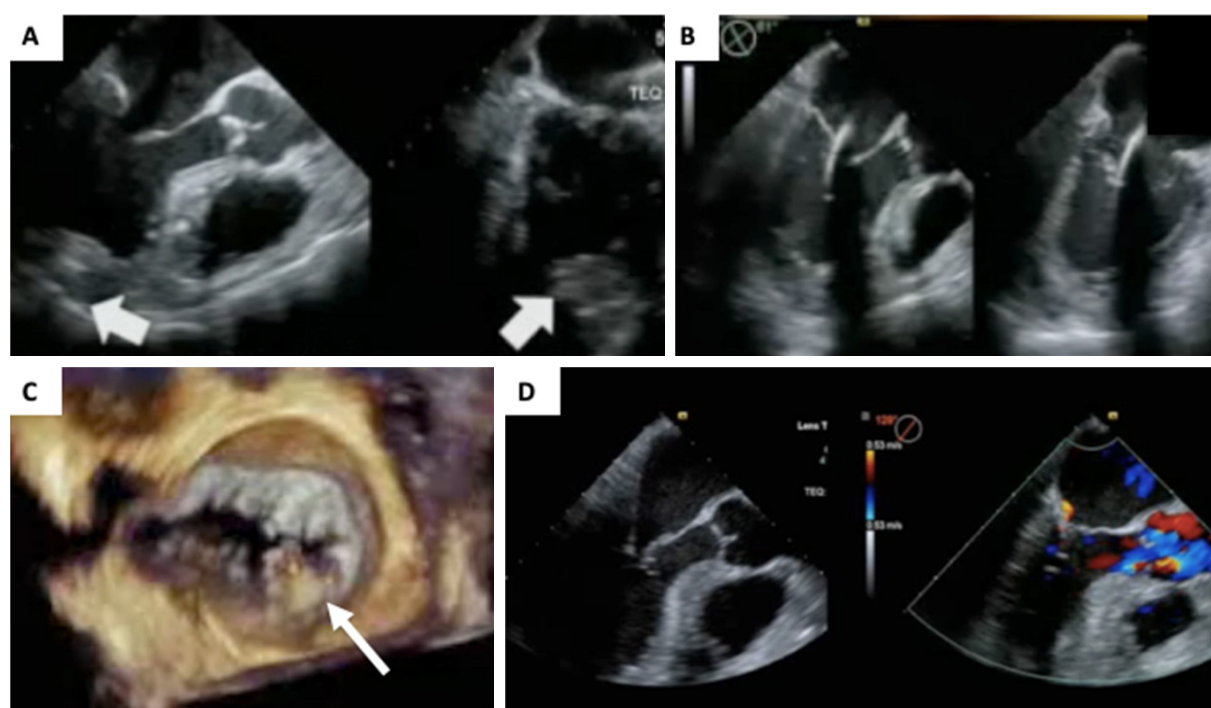


Figure 13. Procedural guidance of the transapical beating heart chordal implantation. A: identification of the LV apex through “finger testing”: the interventionist pushes the apex (white arrow) and the imager checks its position on biplane imaging; B: the system is directed towards the LA on simultaneous biplane LAX and commissural views, avoiding entrapment into subvalvular apparatus. After entering the LA, echocardiographic imaging is switched to 3D surgical view (C), targeting the prolapsing segment (white arrow). After confirmation of leaflet grasping and capture, the device is pulled out from the LV apex and tension is adjusted, until effective MR reduction is shown with color Doppler interrogation (D). LV: left ventricular; LA: left atrium; LAX: long axis; MR: mitral regurgitation

insertion and partial clip detachment, also referred as single leaflet device attachment, and may occur in the case of insufficient leaflet grasping. Depending on the underlying cause, acute MR may require emergency circulatory support and/or bail-out MV surgery;

(5) Iatrogenic mitral stenosis.

CHORDAL APPROACH: TRANSAPICAL BEATING HEART CHORDAL IMPLANTATION

This method applies to all the basic steps of the conventional surgery in which delivery and adjustment of chordal length after implantation is done on the beating heart without the use of the cardiopulmonary bypass.

The most suitable lesion for this approach is an isolated P2 segment flail or with a minimum overriding of at least 9 mm, without significant annular dilatation and severe LV dilatation with leaflets tethering.

Under general anaesthesia a mini-thoracotomy transapical approach is performed under TEE guidance [Figure 13]: the polytetrafluorethylene (ePTFE) chords are delivered to the leaflets and then subsequently adjusted to optimize MR reduction. Two currently available devices are NeoChord DS1000 system (NeoChord, Inc., Eden Prairie, MN)^[17-19] and Harpoon (Edwards Lifescience, Irvine, USA)^[20].

After a standard left lateral mini-thoracotomy in the fifth intercostal space to access the LV apex, the system is directed towards the LA on 2D-TEE guidance (simultaneous multiplane LAX + commissural views) avoiding native subvalvular apparatus entrapment and staying in the central part of the MV (A2-P2 segments). After trans-mitral navigation and entering the LA, echocardiographic imaging is switched



Figure 14. Components of the Cardioband System

to the 3D surgical view, targeting the prolapsing segment. This procedural step relies on specific technical peculiarities to confirm leaflet grasping and capture. After that, the device is finally pulled out from the LV apex and tension is adjusted under real time TEE monitoring till effective MR reduction, avoiding asymmetry of leaflets apposition. Additional chordae could be implanted by repeating the procedure. At the end of the procedure, the apical purse-strings are tied and access site closed.

ANNULAR APPROACH

Transcatheter MV annuloplasty devices, mimicking surgical annuloplasty, restore the normal ratio between the leaflet surface area and the annular area, thus improving leaflets coaptation and can be performed in selected patients as a stand-alone procedure or in one step or double steps combination with other approaches, such as MitraclipTM/chordal implantation^[21,22].

It should be underlined that an appealing feature of this approach is the preservation of the native valve anatomy, thus keeping the option for future MV interventions/re-repair^[23].

Direct annuloplasty

The CardiobandTM device (Edwards Lifesciences, Irvine, California, USA) is an incomplete adjustable surgical-like Dacron band which is trans-septally delivered, and implanted from anterolateral to posteromedial commissure on the posterior annulus under echocardiographic and fluoroscopic guidance.

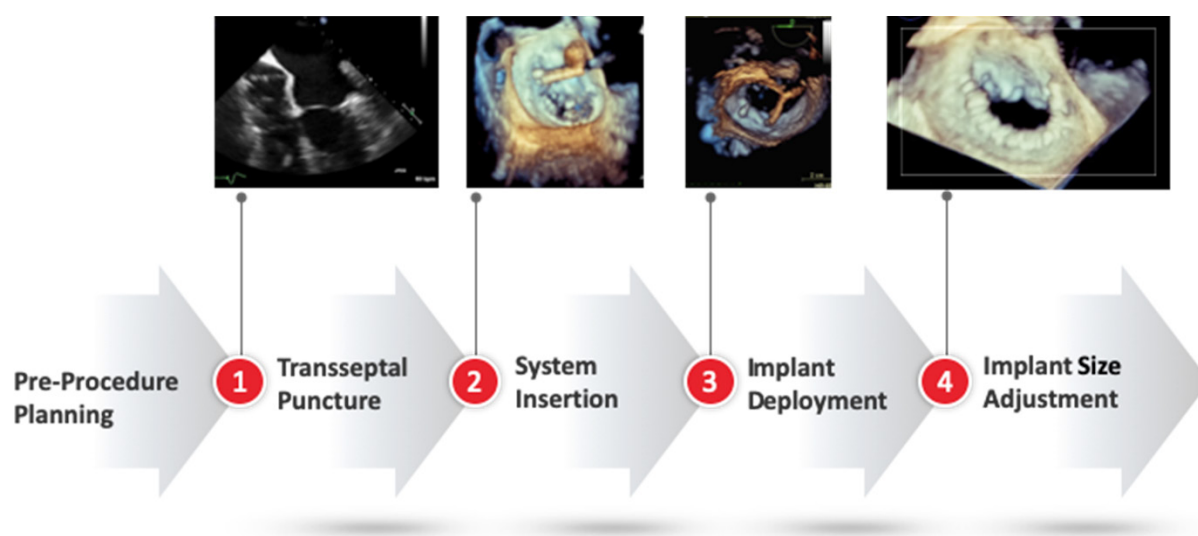
The system is constituted by [Figure 14]: the implant and the anchors.

One of the most important aspect for procedural success is pre-interventional screening based on echocardiography and mostly on CT scan, assessing (1) technical feasibility, mainly based on the relationship between circumflex artery (CA) and posterior annulus to avoid the injury to the artery; (2) annulus sizing and thickness; and (3) the anatomy of LA and IAS.

Pre-procedural CT based planning provides: (1) the coordinates for TSP site; (2) the angle of anchor deployment; (3) the distance from the leaflets hinge point; (4) the distance from CA; and (5) expected fluoroscopic projections.

Intraprocedural monitoring

The implantation of the CardiobandTM (Edwards Lifesciences, Irvine, California, USA) needs to be monitored step by step using a combination of different imaging modalities: 2D and 3D TEE, fluoroscopy and angiography [Figure 15 and Table 2]. As pre-procedural planning is heavily dependent on CT scan, intraprocedural monitoring could be tremendously eased by the upcoming fusion imaging between real time echocardiography and pre-registered CT scan.

**Figure 15.** Procedural steps**Table 2.** Imaging modality for each procedural step

Procedural Step	Imaging modality		TIPS and TRICKS
	Echocardiography	Fluoroscopy	
1. Tailored patient-specific trans-septal puncture	Biplane views: bicaval and SAX views 3D lateral perspective of IAS ME 4-chamber view with retroflexion (height)	AP projection LAO projection	=> TSP must be on top the posteromedial commissure => superior and posterior location in the fossa with a height of 3.5 cm to the annulus (see text for details) => avoid PFO
2. Navigation of the Trans-septal Sheath and Guide Catheter inside the LA	3D overhead of LA	LAO projection	
3. Implant Catheter Placement and Deployment of Anchors	Biplane views and real time Multiplanar Reconstruction 3D overhead of LA	RAO projection Coronary angiography	=> the tip of the catheter should be in contact with tissue along the annulus => distance from the hinge point and implant angle are paramount => rule out circumflex damage
4. Implant Catheter removal and SAT insertion	3D en face view	RAO projection	=> real time 2D color-Doppler: balance between MR reduction and iatrogenic stenosis => careful evaluation of complications (e.g., significant IAS shunt, pericardial effusion, circumflex artery damage)
5. Implant size adjustment/cinching	2D color-Doppler 3D color-Doppler MPR Color-Doppler Pressure gradient MPR valve area and annular remodeling	RAO and LAO projections	

SAX: short axis; AP: antero-posterior; LAO: left anterior oblique; IAS: interatrial septum; PFO: patent foramen ovalis; RAO: right anterior oblique; LA: left atrium; MPR: multiplanar reconstruction

Transseptal puncture and Transseptal Sheath insertion

The optimal TSP site is pre-defined by CT planning which provides data regarding the distances from muscular part in bicaval view, from aorta in SAX-B view and the height from annular plane in four-chamber view. In particular the puncture site must be above the posteromedial commissure: this is best appreciated on the 3D overhead perspective of LA or en face view of the IAS from LA [Figure 16]. The height of the TSP must be > 3.5 cm from annular plane, as measured in four-chamber view.

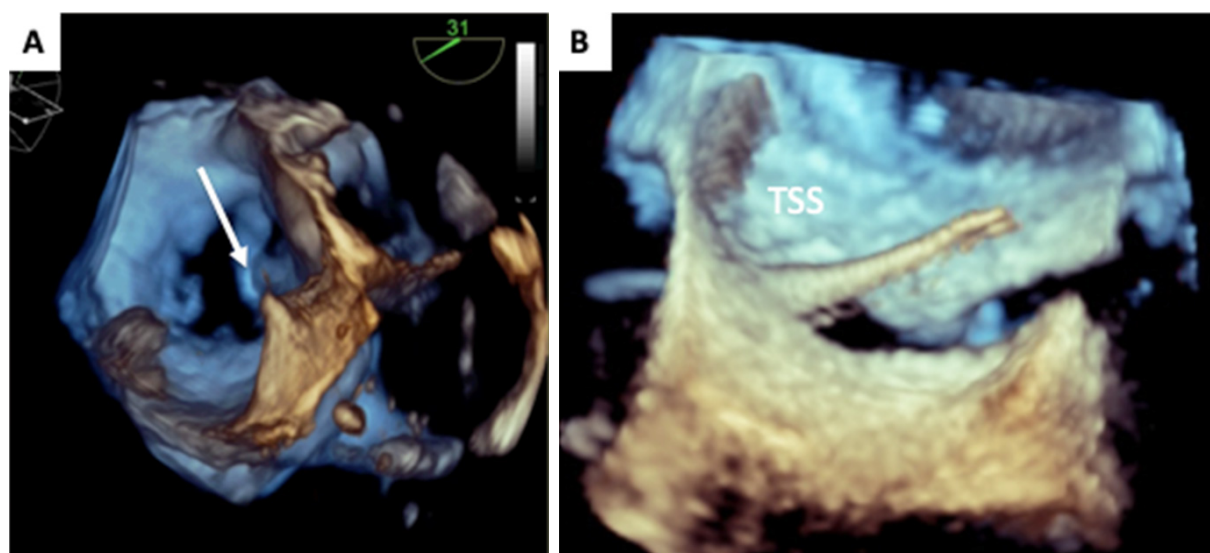


Figure 16. Transseptal puncture. A: posteromedial commissural perspective: tenting (white arrow) must be located exactly above the posteromedial commissure; B: 3D lateral perspective of LA showing the TSS across the septum (with the dilator) inside the LA. TSS: transseptal steerable sheath; LA: left atrium

Navigation inside left atrium and Implant deployment

Different 3D perspectives and fluoroscopic LAO CAU view enable visualization of the system in the different annular segments and the steering of implant delivery system (IDS) inside the LA along the posterior annulus [Figures 17 and 18]. After reaching the target point, the implant catheter (IC) is advanced to contact the annulus: several 2D and biplane views or 3D multiplanar reconstruction allow verification of the location of the tip of IC in the different annular segments, in terms of proper distance from the hinge point of posterior leaflet and device angulation in relation to the annulus.

Anchoring should be close to the leaflet hinge point in order to effectively remodel the annulus. The first anchor should be as anterior as possible, closest to the anterior trigone. After confirmation of the location with 3D overhead LA perspective, coronary angiography is performed to rule out the risk of CA injury. The anchor is then released following verification of proper anchoring through a push-and-pull test under 2D echocardiographic and fluoroscopic (RAO view) guidance. As the first 3 anchors operate as a root foundation for the procedure, they are implanted close to each other. The Cardioband™ implant is deployed until the radiopaque marker of the IC reaches the next marker on the implant itself. The IC tip is then navigated to the next anchoring point along the posterior annulus using echocardiographic guidance (3D overhead perspective), until the IC reaches the last anchoring site on the posterior trigone. 3D overhead perspective of MV is useful for guiding positioning and gross movement of the IDS along the mitral annulus, as the band is gradually deployed, anchor by anchor. Live 3D multiplanar reconstruction is of utmost importance for fine adjustment of IDS trajectory/angle in relation to the annular shelf and for fine positioning of the annulus for safe and effective anchor deployment.

IDS removal and size adjustment tool insertion

After the last anchor deployment and disconnection from the IDS, the size adjustment tool (SAT) is inserted through the transseptal steerable sheath until its distal end reaches the adjustment spool of the implant under 3D echocardiographic and fluoroscopic guidance.

Implant size adjustment and cinching

After SAT connection, the implant is contracted by rotation of the adjustment roller: reduction of MR severity assessed by color-Doppler and reduction of annulus size are monitored [Figure 19]. Appropriate

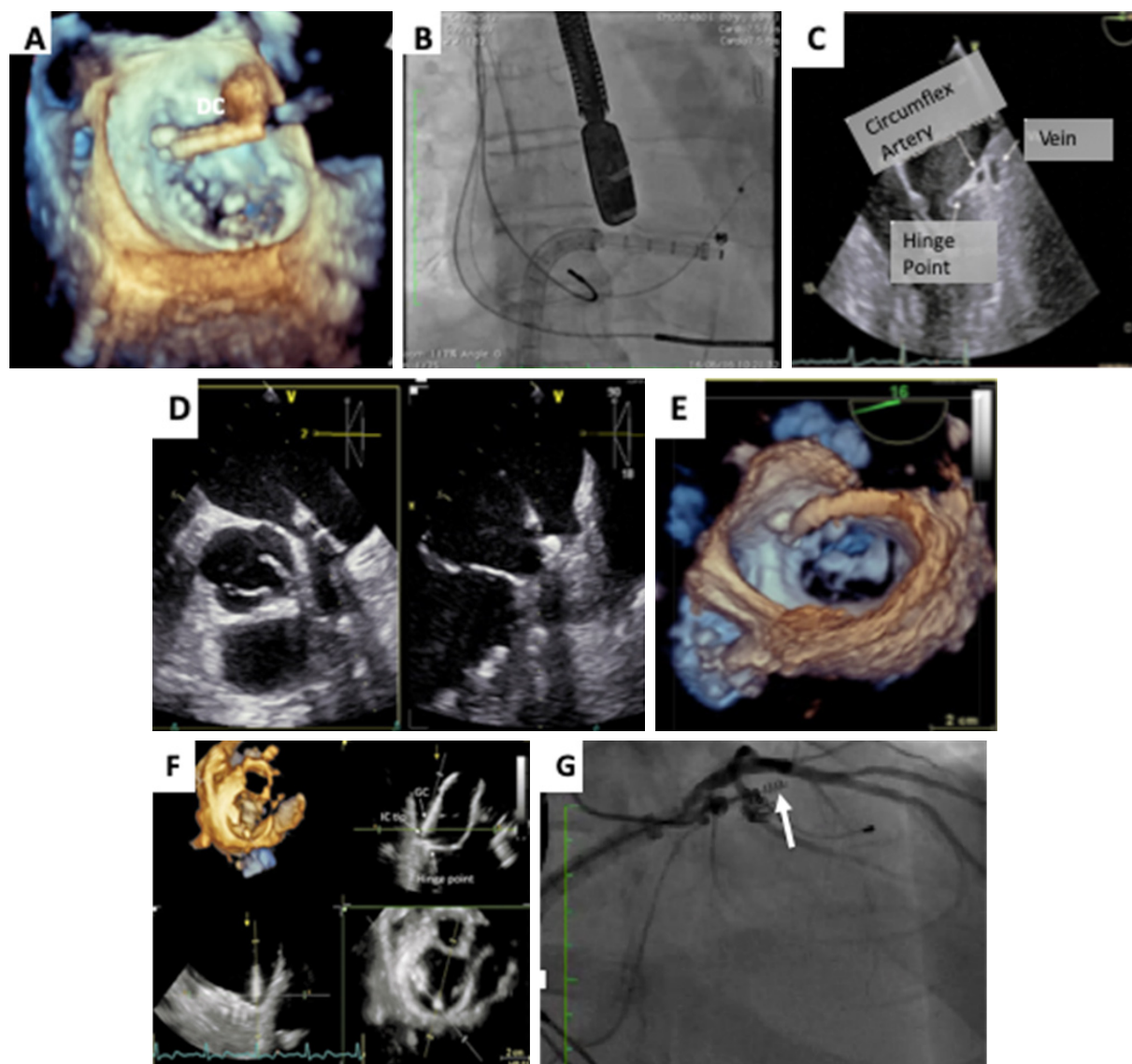


Figure 17. Navigation inside left atrium and Implant deployment. DC positioned at level of anterior commissure: A: 3D overhead perspective; B: AP fluoroscopic projection; C: echocardiographic localization of circumflex artery; D: biplane imaging for fine tip positioning on the annulus and assessing the local angle of approach to the annulus; E: 3D MV en face view showing spatial relationships during deployment of first anchors in antero-lateral commissural area; F: multiplanar reconstruction showing anchor delivering; G: coronary angiography: spatial relationship between anchor (white arrow) and circumflex artery. DC: delivery catheter; AP: antero-posterior; MV: mitral valve

implant size is a compromise between adequate MR reduction without iatrogenic mitral stenosis. The SAT is then detached leaving the implant with the desired degree of contraction.

Assessment of results and detection of complications

Following the MitraclipTM procedure, a multi-modal approach is most appropriate to characterize and quantify residual MR. Particular to this procedure is the final assessment of mitral annular remodeling of which 3D multiplanar reconstruction seems to be the best method.

Percutaneous MV direct annuloplasty is generally a safe and effective procedure even in high-risk patients and is associated with few major complications^[23].

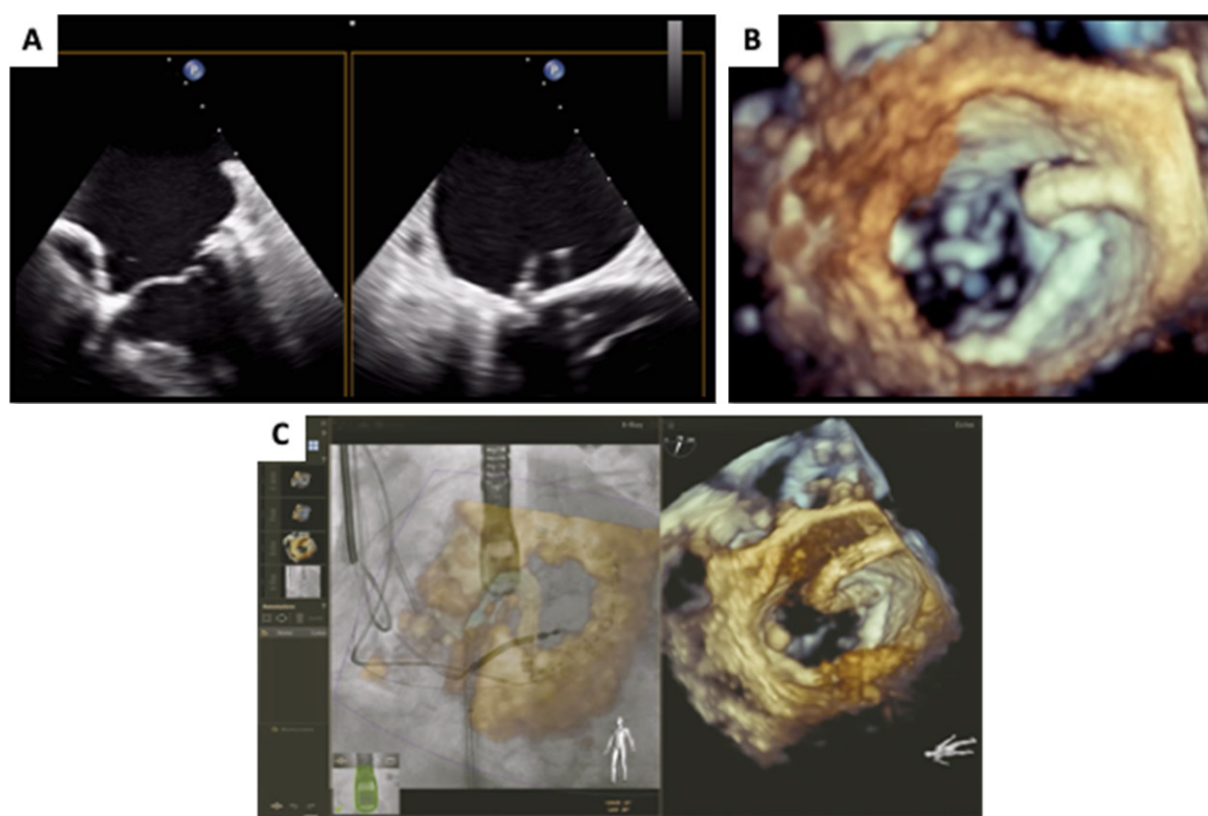


Figure 18. Last anchors deployment. A: 2D biplane views (starting at 60°): 2D echo image quality is usually sub optimal at the postero-medial commissure; B: 3D surgical view and (C) fusion imaging superimposed to the LAO CAU fluoroscopic view showing deployment of the last anchors. LAO: left anterior oblique; CAU: caudal

Annular Cinching by 10% Annular Cinching by 20% Annular Cinching by 40%

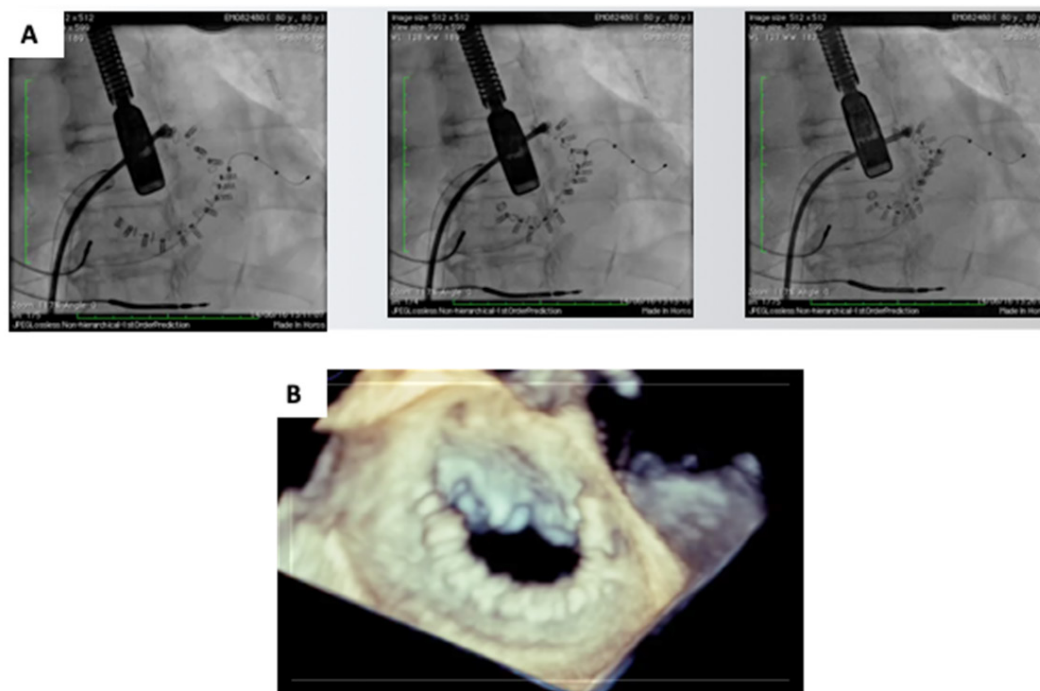


Figure 19. Cinching and final result. A: LAO fluoroscopic projection at different degrees of cinching; B: 3D en face view showing final result. LAO: left anterior oblique

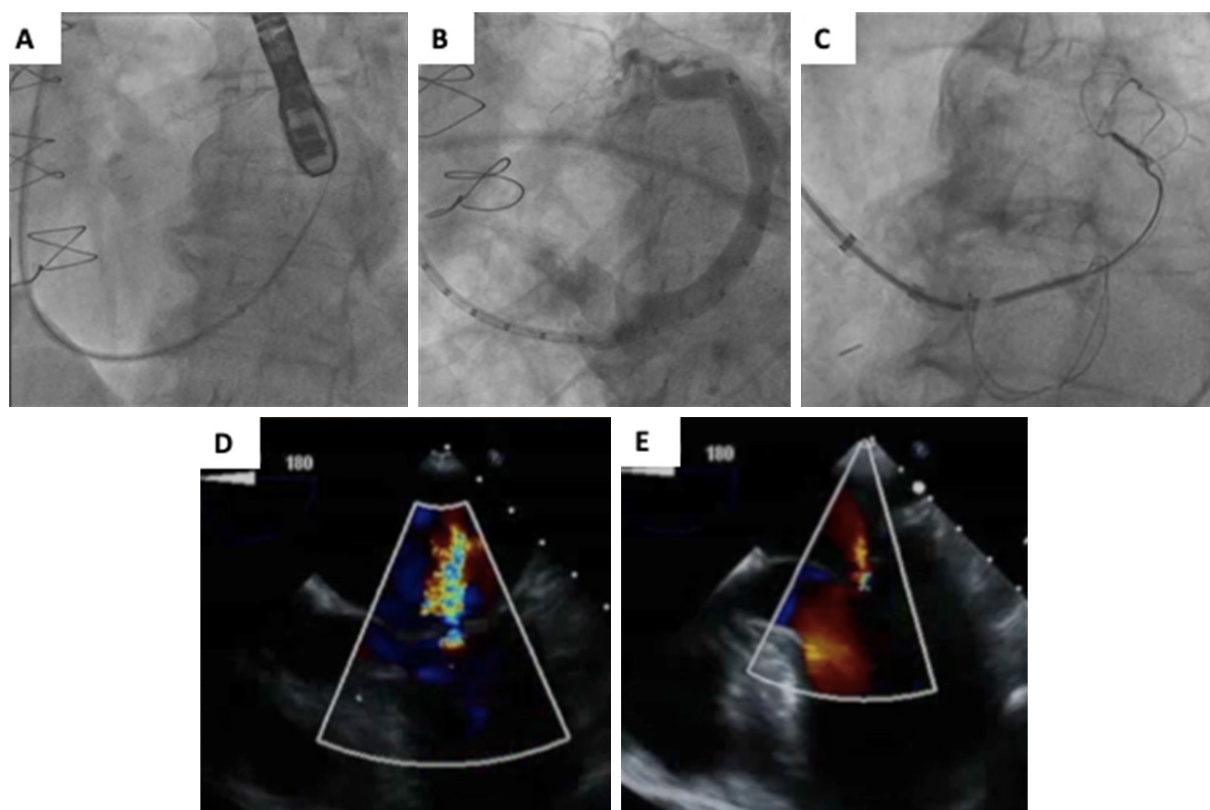


Figure 20. Procedural guidance of Coronary Sinus Annuloplasty. After cannulation of the CS, a delivery catheter is positioned distal in the CS/GCV (A), as close as the antero-lateral commissure of the MV; quantitative venography (B) and pre-procedural CT allows for selection of the appropriate implant size. After deployment of the distal anchor of the device and application of manual traction, the proximal anchor is deployed (C); reduction of the septo-lateral dimensions and MR downgrading are finally assessed by fluoroscopy and color Doppler imaging: pre-procedural (D) and post-procedural MR (E). CS: coronary sinus; GCV: great coronary vein; CT: computed tomography; MV: mitral valve; MR: mitral regurgitation

Transfemoral indirect annuloplasty: coronary sinus annuloplasty

Indirect annuloplasty through the coronary sinus re-shapes the anteroposterior MV annular dimensions to improve mitral leaflet apposition and thus coaptation, due to close relationship between the coronary sinus (CS)/great cardiac vein (GCV) and the posterior part of the MV annulus.

The CarillonTM Mitral Contour System (Cardiac Dimensions, Kirkland, WA, USA), is the most clinically tested indirect annuloplasty device, consisting of two helical anchors connected by a nitinol bridge.

The AMADEUS study reported implantation feasibility without significant MR improvement in a small population while undertaking a moderate risk of coronary complications^[24] while the TITAN trial reported successful implantation leading to MR reduction in 36 of 53 enrolled patients with subsequent LV reverse remodelling^[25].

Using the right internal jugular access, the distal anchor is positioned in the CS/GCV, and subsequent traction is applied to re-shape the septo-lateral MV annular dimensions, using a combination of fluoroscopy, as the main imaging modality, and TEE or transthoracic monitoring as adjuncts, mainly used for final procedural assessment [Figure 20]. A LAO caudal projection, the fluoroscopical short axis of the MV, shows the CS surrounding the posterior part of the MV.

After cannulation of the CS, a 9F delivery catheter is positioned distal in the GCV, as close as the antero-lateral commissure of the MV. Then the arteriovenous anatomy is characterized through occlusive venography and coronary angiography, allowing for the selection of the appropriate implant size. After the distal anchor of the device is deployed, manual traction is applied to reshape the periannular tissue. Ultimate device size and position are determined by maximal geometric reduction of the septo-lateral dimensions and reduction of MR, as assessed by fluoroscopy and TEE (mainly mid-esophageal views and 3D MV en face view). Before final release, coronary angiography rules out coronary injuries/preservation of coronary flow. The implant can be recaptured and repositioned. Procedural success strongly relies on the variable distance/relationship between the CS and the posterior MV annulus, influencing effective annular cinching.

CONCLUSION

Percutaneous MV therapies are increasingly emerging as safe alternatives for high-risk patients not suitable for conventional open-heart surgery. Intraprocedural monitoring relies on the sapient integration of fluoroscopy and echocardiography, highlighting the importance of the communication inside the cath lab between the interventional imager and the interventional cardiologist in order to perform more effective and safer procedures.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Ancona F, Stella S, Capogrosso C, Agricola E

Performed data acquisition, as well as provided administrative, technical, and material support: Melillo F, Ingallina G, Boccellino A, Napolano A

Availability of data and materials

Not applicable.

Financial support and sponsorship

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

A written informed consent for publication was obtained.

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Technical Note

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Robotic Heller myotomy

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Abstract

Achalasia is a neurodegenerative disorder of the esophagus of unknown etiology, which affects motility, causing symptoms such as progressive dysphagia with liquids then solids, heartburn, regurgitation, odynophagia, weight loss, nocturnal cough, and chest pain. Evaluation will show a characteristic “bird’s beak” appearance on barium esophagram and diagnosis is confirmed with esophageal manometry. Durable relief from the symptoms of achalasia can be achieved with pneumatic dilation, per-oral endoscopic myotomy, or surgical myotomy. Laparoscopic Heller myotomy with Dor (or Toupet) fundoplication for many years had been considered the gold standard for therapy. Since its development in 2001, the robotic Heller myotomy (RHM) has gained increasing popularity. Studies have shown equivalent efficacy of relieving achalasia symptoms but decreased incidence of esophageal perforation with RHM. The higher cost of RHM remains the largest barrier. Our objective was to provide a brief review of the current literature related to RHM and provide a detailed description of how to perform the procedure.

Keywords: Heller myotomy, achalasia, robotic, surgical treatments for achalasia, minimally invasive surgery

INTRODUCTION

Achalasia is a neurodegenerative disorder of the esophagus characterized by failure of the lower esophageal sphincter (LES) to relax and decrease or absence of esophageal body peristalsis^[1-3]. The incidence has variable reports, but meta-analysis estimates that it affects 0.5 to 1.2 persons per 100,000 per year^[3,4]. Achalasia can affect both genders, all races and all ages. A few studies have suggested that disease risk increases



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age, whereas other studies describe a bimodal incidence by age with peaks around ages 30 and 60 years^[1-6]. The etiology of achalasia remains unclear, although it is purported to be multifactorial. The most common form of achalasia is idiopathic.

Although rare, achalasia is likely the best described primary esophageal motility disorder with clear clinical, manometric, endoscopic and radiologic findings^[2,3]. Commonly reported symptoms associated with achalasia include progressive dysphagia with liquids and then solids, heartburn, regurgitation, odynophagia, weight loss, nocturnal cough and chest pain. Manometry is the gold standard for diagnosis of achalasia into 3 subtypes with different manometric patterns: Type I (classic achalasia of aperistalsis and failure of the LES to relax), Type II (with esophageal compression) and Type III (spastic achalasia) as defined by the Chicago classification^[3,7]. Endoscopy will demonstrate food particles in the absence of a mucosal stricture and a narrowed gastroesophageal junction, the latter of which is well learned as the “bird’s beak” appearance on barium esophagram^[3,7].

The treatment of achalasia is not curative. It is a progressive disease that leads patients to seek symptom palliation, which can be accomplished by reducing the resting and swallow-induced pressures of the LES^[1,3,7-10]. That is, therapy is aimed at relieving the functional obstruction. This can be done with medical, endoscopic and surgical therapies. Medical therapies include drugs such as nitrates and calcium channel blockers that act to relax smooth muscle^[3,7]. Endoscopic sphincteric injection of Botox has also been performed with limited and variable success rates, whereas graded pneumatic dilation has more robust results^[7,11]. In comparison, minimally invasive Heller myotomy is currently the gold standard surgical approach for achalasia as it has the best long-term outcome. Although per-oral endoscopic myotomy (POEM) and robotic Heller myotomy (RHM) are increasingly being used, laparoscopic Heller myotomy (LHM) is the longest practiced surgical approach with safe and effective outcomes^[8,9,12-15].

With recent advancements in technology, RHM has become an alternative option for the treatment of achalasia. It was first described in 2001 in a case report by Melvin *et al.*^[16]. At this point, outcomes are somewhat controversial for RHM compared to LHM; however, many studies report that it is equivalent to LHM in terms of achieving the desired result of symptomatic relief but with fewer complications related to mucosal perforation^[9,13,14,17-20]. Cost remains one of the largest barriers to overcome in robotic operations; however, cost reduction strategies can be further explored with increased utilization^[10,17,19,21].

ROBOTIC HELLER MYOTOMY AND PARTIAL FUNDOPLICATION

Perioperative preparation, positioning and port placement

The patient is placed supine on the operating room table with both arms tucked at the sides. Foot boards should be secured at the end of the table to prevent the patient from sliding down the table. A dose of perioperative antibiotics (first-generation cephalosporin) is administered within 1 h of incision. After induction with general anesthesia, a single-lumen endotracheal tube is used for intubation. Upper endoscopy is then performed and the scope left in the stomach with the light turned off. The patient’s abdomen is then prepped and draped in a sterile manner.

The Da Vinci Xi surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) is used for our operation. A total of 5 or 6 ports can be used for this procedure. Afaneh *et al.*^[17] describe a 5-port set up transversely across the abdominal midline. The first port is placed in the midline roughly 15 cm below the xiphoid process. Three additional 8-mm robotic ports and a 5-mm retractor port are then placed^[17]. A case report in the pediatric population also describes a 4-port method^[22]. We elect to use 6 ports during our procedure. Port location is shown in Figure 1. The first port is placed in the right lower quadrant using the Optiview technique with a 12-mm port. Intraperitoneal insufflation with carbon dioxide is set to a target pressure of 15 mmHg. This 12-mm port is used by the bedside assistant for passage of suture, suctioning, and

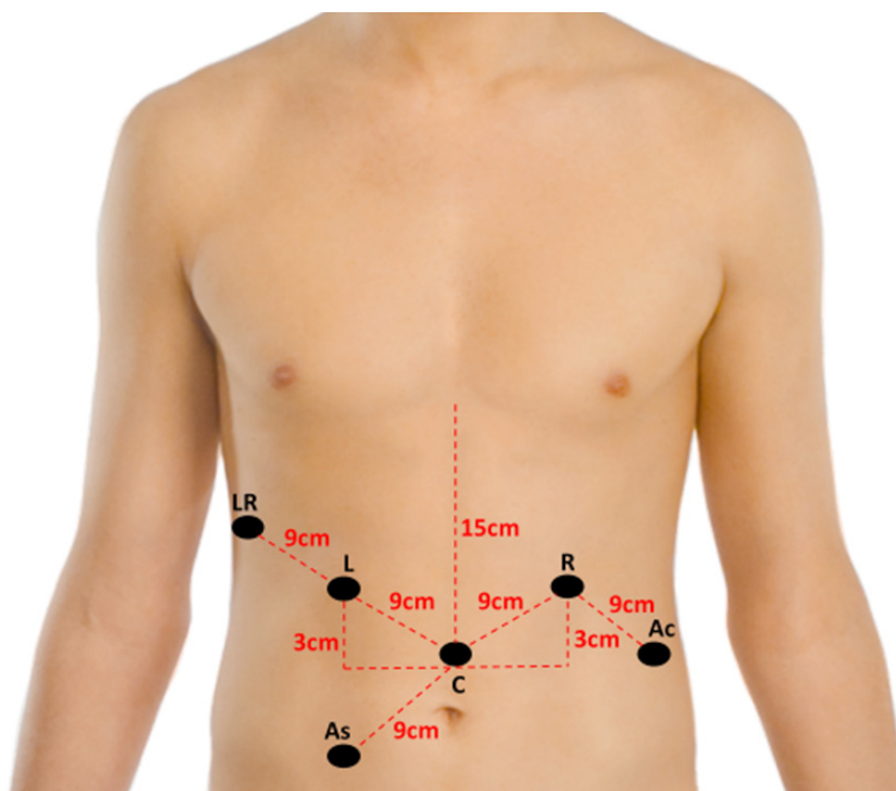


Figure 1. Location of ports for robotic Heller myotomy. LR: liver retractor port; L: port for left robotic arm (arm 1); C: camera port (arm 2); R: port for right robotic arm (arm 3); Ac: port for accessory robotic arm (arm 4); As: port for bedside assistant. Image created using public domain photo from Wikipedia Commons, 2008^[23]

rolled-up gauze pads. Four 8-mm robotic ports and a 5-mm liver retractor port are then placed. The liver retractor port is placed as laterally as possible, just under the right costal margin. This location prevents collisions between the robotic arm and the liver retractor, as opposed to the typical subxiphoid location. The patient is positioned in reverse Trendelenberg and the liver retractor put into appropriate position prior to docking. The 0-degree camera is used for the Optiview port access. A 30-degree camera is used for the rest of the operation via the robotic arm 2. Cadere forceps are used in the left robotic arm (arm 1), and the curved bipolar dissector, vessel sealer, and fenestrated forceps are used in the right robotic arm (arm 3), while the tip-up fenestrated forceps are used in the accessory robotic arm (arm 4), which is located to the surgeon's right (patient's left) of the right robotic arm. The camera port is located 15 cm caudal from the xiphoid process, typically in a supraumbilical position. Arms 1, 3, and 4 are then staggered as shown in Figure 1, located 9 cm apart from one another. At times, in small patients, a distance of 8 cm between ports is required which is also acceptable. Arms 1 and 3 are located such that they are at least 3 cm cranial compared to the camera port, as this facilitates working high in the mediastinum.

Exposure of the distal esophagus

The operation begins with division of the gastrohepatic ligament. The area overlying the right crus is cleared off, just below the gastroesophageal junction, and extending across and dividing the phrenoesophageal ligament. If performing an anterior or Dor partial fundoplication, only the anterior aspect of the esophagus should be dissected to leave as much of the phrenoesophageal ligament intact. This is in contrast to a posterior or Toupet partial fundoplication where the esophagus is mobilized circumferentially by clearing the retroesophageal window. The left crus is then identified and dissected out. The method of esophageal exposure is consistent with prior literature description^[17,24-26].

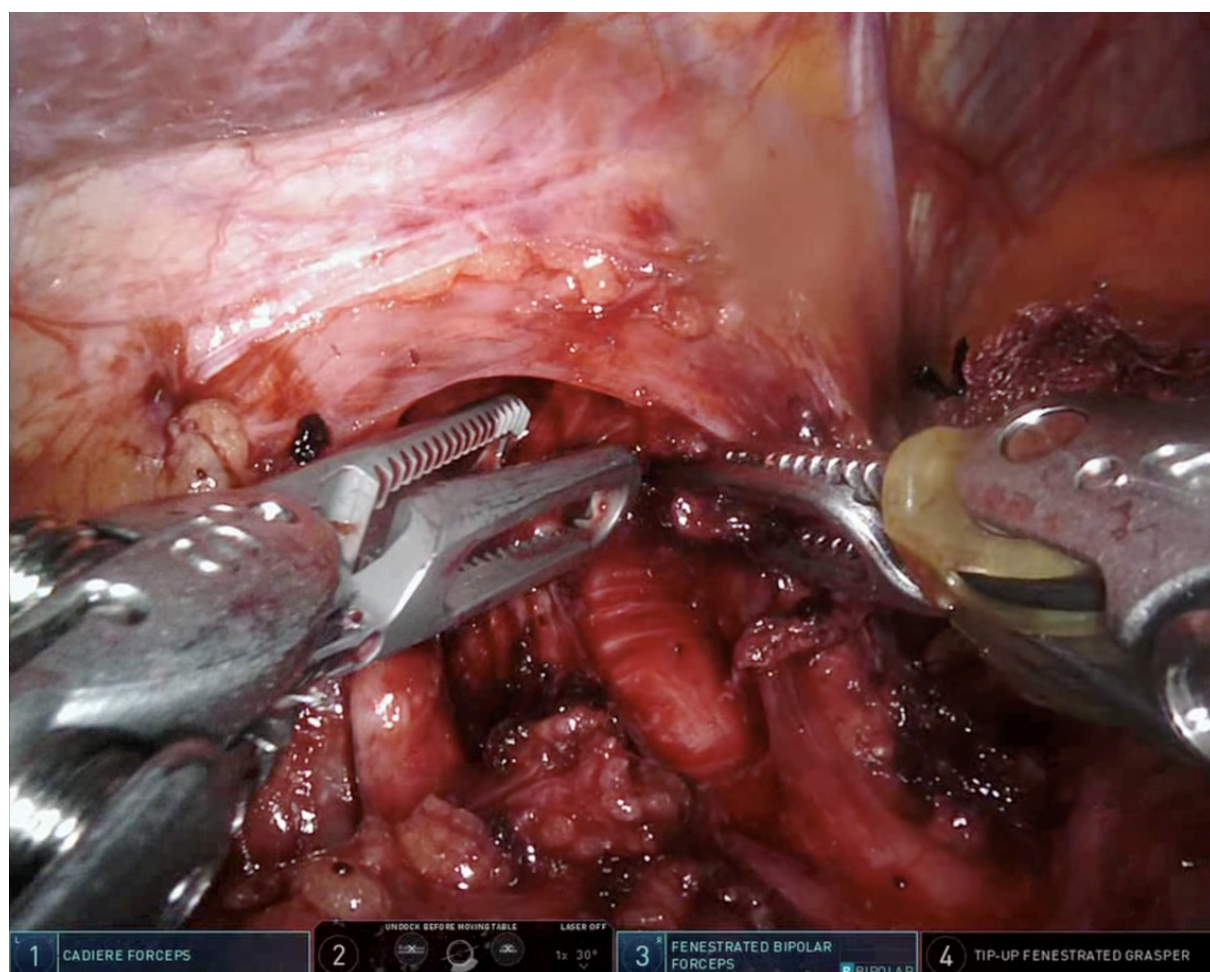


Figure 2. The use of Cadiere forceps and fenestrated bipolar forceps to perform myotomy with blunt dissection

Mobilization of the gastroesophageal junction

The periesophageal space is bluntly dissected anteriorly well up into the mediastinum. The esophagus should be mobilized for at least 8 cm of length. During this part of the procedure, care should be taken to identify and preserve the vagus nerve.

Heller myotomy

The myotomy usually begins between 11 and 1 o'clock on the esophageal side^[17,26]. There are various techniques for creating the myotomy; we prefer to use Cadiere forceps in the left robotic arm and a fenestrated bipolar forceps in the right robotic arm to pull the fibers apart, and use electrocautery and energy near the mucosa very sparingly to avoid thermal injury [Figure 2]. The longitudinal and circular muscle fibers are divided until the submucosa underneath is exposed. This should be carried out for roughly 6-8 cm up into the chest and about 3 cm onto the stomach. It is important to disrupt any and all muscle fibers along the myotomy; at times, vessels crossing the submucosa can masquerade as muscle fibers. Special caution should be taken when extending the myotomy onto the stomach, as the differentiation between muscle fibers and submucosa is more difficult to appreciate, and the muscle fibers tend to be more adherent to the submucosa. Methylene blue is instilled into the esophageal lumen after the myotomy is complete to ensure there was no mucosal perforation. Alternatively, the patient can be placed in Trendelenburg, the esophagus and esophagogastric junction submerged under water or saline, and the esophagus insufflated to detect a leak, although this can be cumbersome unless the robotic-integrated bed

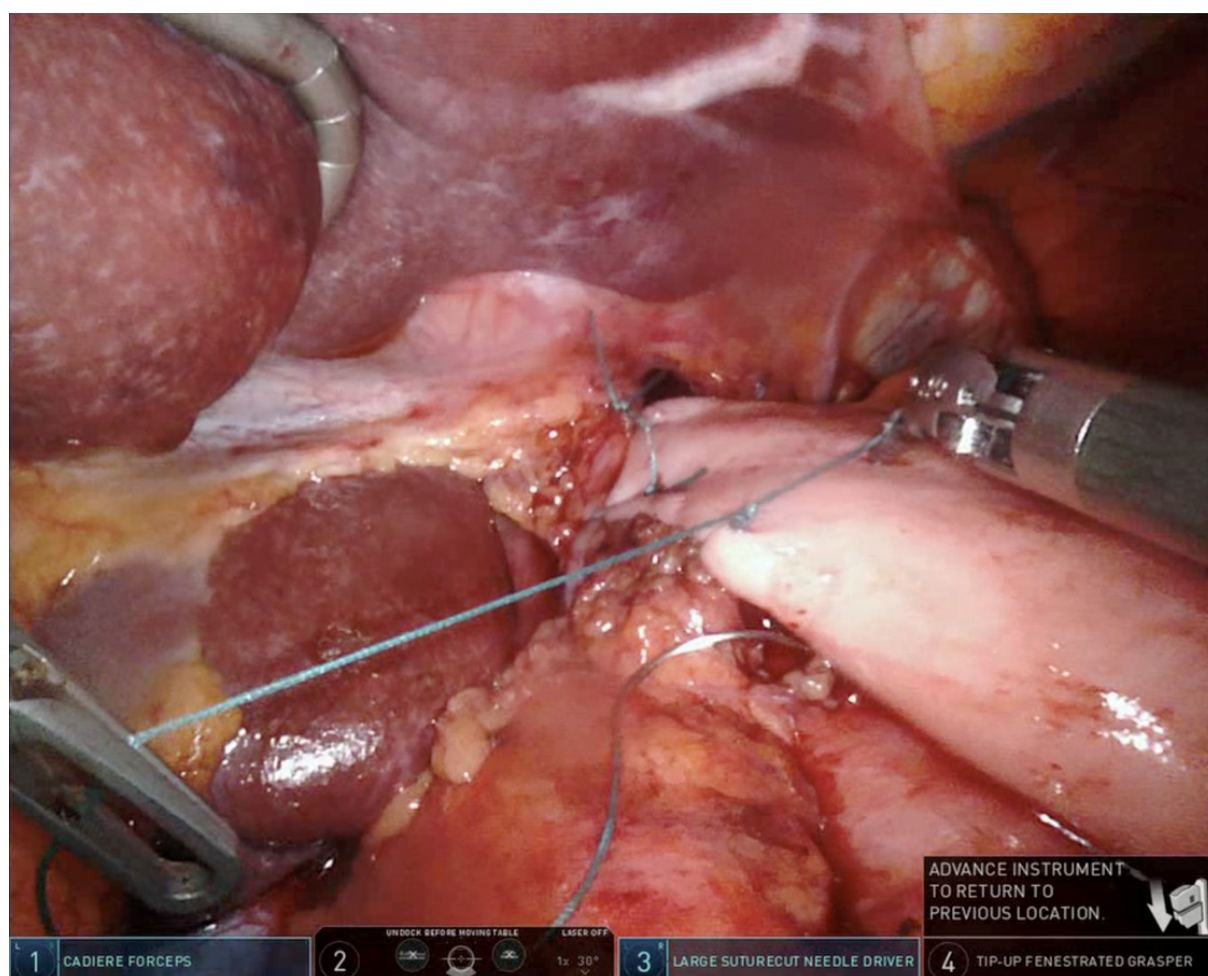


Figure 3. Completion of right-sided sutures for Dor fundoplication

is used^[26]. Previous studies have cited the utilization of endoscopic balloon inflation across the EGJ during this portion of the procedure for visualization of planes with some success^[27].

Fundoplication

In preparation for fundoplication, the stomach is retracted medially and the short gastric vessels dissected and ligated using a vessel sealer. For the Dor anterior partial fundoplication, posterior dissection is not necessary thereby avoiding injury to the posterior vagus nerve. The number of stitches used and exact placement may vary by surgeon. At our institution, we first use two 2-0 Ethibond sutures to secure the fundus, esophagus and left crus together; the fundus is then rolled over the esophagogastric junction, and two 2-0 Ethibond sutures are placed similarly on the right side [Figure 3]. We avoid placing the sutures of the fundoplication too far posteriorly, so as not to overly narrow the hiatus. An additional suture may be used to secure the fundus to the diaphragm at the top of the hiatus. Studies have shown fundoplication to be a necessary part of the procedure to mitigate reflux-related symptoms^[28]. The choice of Dor vs. Toupet fundoplication shows no significant difference in outcomes and is therefore left up to the surgeon's decision-making based on their individual experience^[29]. The hypothetical benefits of the Dor are a decreased risk of dysphagia and that the fundus covers part of the myotomy and buttresses it in case a small unrecognized mucosal injury occurs. The hypothetical benefits of the Toupet are improved reflux control and that the fundoplication pulls apart the muscle edges of the myotomy, preventing it from healing together and causing recurrent symptoms.

Technical considerations

The technical advantages of the use of robotic operative systems are mainly enhanced visualization and enhanced degree of movement available. In consideration of taking advantage of these benefits, it is important to keep your visual field free of blood^[17]. This can be achieved with the proactive use of hemostatic devices to ensure vessels are coagulated prior to disruption. Additionally, it is important to ensure adequate mobilization of the gastroesophageal junction and the gastric fundus to effectively perform all steps of the procedure. Additionally, the tools utilized allow for precise dissection during the myotomy. The camera and dissectors can be used to ensure complete disruption of the LES muscle fibers^[17].

Postoperative management

Upon completion of the procedure the patient should be extubated in the operating room. When stable, they can be moved to the Post-Anesthesia Care Unit (PACU) and a postoperative chest radiograph should be obtained. If the patient is in stable condition, they can be sent to the floor from the PACU with orders for scheduled anti-emetics to prevent retching, maintenance fluids, pain management, aggressive pulmonary toilet, and a clear liquid diet. Avoiding postoperative retching is important for maintaining the integrity of tissues manipulated by the operation^[17]. On postoperative day 1, a water-soluble barium esophagram is obtained to ensure no esophageal leaks are present. Orders for the clear liquid diet should be maintained until the patient passes the postoperative swallow study. If the patient passes the swallow study, tolerating liquid diet, voiding appropriately, and if pain is controlled, he/she can be discharged as early as postoperative day 1. The patient should be allowed slow progression from full liquid to soft food diet over the next 2-4 weeks^[27]. Follow-up is scheduled for 1 month. At that time, the patient can be allowed to advance diet as tolerated and resume exercise, provided there are no complications.

REVIEW OF LITERATURE: ROBOTIC HELLER MYOTOMY

Since the first published case report of an RHM in 2001, much of the literature has sought to evaluate the efficacy and safety of the robotic approach when compared to the already established laparoscopic approach. These data are summarized in Table 1. Multiple studies have compared data between LHM and RHM and revealed that there are no statistical differences in estimated blood loss (< 50 mL), operative time, or perioperative mortality^[13,17,20]. Although operative time does not show statistically significant differences, the robotic approach has been shown to be slightly longer (122 min vs. 133 min)^[13]. Other reports have broken down operative time relative to the number of cases performed and have shown association with improved times as the surgeon performs more cases^[17]. This alludes to the potential for the robotic approach to become shorter in length as surgeons gain further experience. Although similar to LHM in many categorical results, in some studies, RHM was associated with a shorter length of hospital stay [(1 days vs. 2 days), (2.42 days vs. 4.42 days)]^[13,17].

When considering the operative surgical goal for achalasia, RHM is effective in achieving symptomatic relief without producing significant morbidity. Each case report indicates short-term post-operative relief of dysphagia symptoms^[22,24,25,32]. Two larger studies of greater than 50 patients reported a 92.4% and 100% rate of relief for dysphagia symptoms following operation with 80% of patients needing no further intervention^[13,27]. In comparison to LHM, Kim *et al.*^[14] suggests that the technical advantage of the robotic approach allows for a longer myotomy incision, resulting in greater durability of symptomatic relief for dysphagia. The most frequently reported long-term symptom following this procedure is reflux, which requires medication control at a rate of 62%; however, this showed no significant difference compared to the laparoscopic procedure^[13].

Safety is of course the next major consideration of this operation. RHM is associated with very few postoperative or perioperative complications. The rate of esophageal mucosal perforation is of primary consideration throughout the literature. There are no noted mucosal perforations in any of the case reports

Table 1. Summary of data from retrospective studies

Ref.	Type of procedure	No. of patients	Operative time (min)	LOS (days)	Risk of perforation (%)	Cost (\$)
Shaligram <i>et al.</i> ^[10] 2012	RHM	149	-	2.42 ± 2.69	-	9,415 ± 5,515 ^a
	LHM	2116	-	2.70 ± 3.87	-	7,441 ± 7,897 ^a
Villamere <i>et al.</i> ^[30] 2015	RHM	314	-	2.26 ± 2.05 ^a	-	9,258 ± 4,278 ^a
	LHM	3135	-	2.78 ± 3.55 ^a	-	7,425 ± 5,693 ^a
Perry <i>et al.</i> ^[13] 2014	RHM	56	133 ± 29	1 ^a	0.0 ^a	-
	LHM	19	121 ± 22	2 ^a	16.0 ^a	-
Kim <i>et al.</i> ^[14] 2019	RHM	37	158	2.02	2.7	-
	LHM	35	157	2.17	11.4	-
Ali <i>et al.</i> ^[15] 2019	RHM	44	183.5 ^a	1	0.0 ^a	-
	LHM	40	157 ^a	1	15.0 ^a	-
	POEM	87	169	1	1.1	-
Huffmann <i>et al.</i> ^[18] 2007	RHM	24	355 ± 23 [†]	2.8	0.0	-
	LHM	37	287 ± 9 [†]	2.6	8.1	-
Khashab <i>et al.</i> ^[21] 2017	RHM	52	263 ^b	2.3	0.0	17,782 ^b
	POEM	52	106 ^b	1.9	7.7	14,481 ^b
Pallabazzer <i>et al.</i> ^[27] 2020	RHM	66	161.4 ± 40.2	-	-	-
Saurabh <i>et al.</i> ^[31] 2014	RHM	12	150	1.5	-	-

Meta-analyses, case reports, and case series not included in this chart. ^aIndicates that there was statistically significant difference ($P < 0.05$) in data when RHM was compared to LHM; ^bIndicates that there was statistically significant difference ($P < 0.05$) in data when RHM was compared to POEM; [†]operative time for this study was measured as time of anesthesia induction to extubation. LOS: length of stay; RHM: robotic Heller myotomy; LHM: laparoscopic Heller myotomy; POEM: per oral endoscopic myotomy

and only 1 perforation noted in the retrospective reviews^[14,15,21,22,24,25,27,32]. In a review of the progression of the role of myotomy, Allaix and Patti^[33] highlight two separate studies that show rates of mucosal perforation in LHM being 16% and 8%, while the RHM groups had a 0% perforation rate in both studies. A meta-analysis further confirmed the safety of RHM in view of the significantly fewer mucosal injuries, and stated that it is safer than the laparoscopic approach^[20]. As mucosal perforation leads to greater perioperative morbidity, the evidence reported in these studies should be strongly considered when thinking of the safety of the patient in choosing the operative approach.

The technical advantages to this procedure are believed to be associated with the enhanced 3-D visualization and the increased degree of movement of the surgical instruments with robotic systems^[13,31,34]. The enhanced visualization and increased precision of control are believed to contribute to having fewer mucosal perforations and to the ability to make longer incisions for the myotomy^[13,14,31]. In consideration of disadvantages of robotic operations, multiple studies cite cost. The cost analyses performed show statistically significant higher cost when comparing RHM to LHM, with one study citing as much as a 21% increase when comparing robotic to laparoscopic surgeries^[17,19,21,30]. One multicenter study demonstrated that LHM was significantly less expensive than RHM (\$7,441 vs. \$9,415, $P = 0.0028$)^[10]; another found a similar difference (\$7,425 for LHM vs. \$9,258 for RHM, $P < 0.05$)^[30]. Further efforts should be made to analyze cost associated with robotic procedures and discover ways to mitigate charges to help overcome this barrier.

Most of the research on RHM is retrospective in nature and with small cohorts, posing some limitations regarding prospective application of the data. However, enough evidence has been derived from these studies to provide grounds for further investigation. Future randomized control studies are needed for confirmation of suspected outcomes.

CONCLUSION

RHM with Dor (or Toupet) fundoplication is an extremely safe and effective procedure for relieving symptoms of esophageal achalasia. Use of this approach is associated with almost no complications related

to esophageal perforations. In our experience of 50 patients undergoing this operation, we experienced a 0% perforation rate, median hospital stay of 1 day (range 1-3 days), median operation duration of 143 min (range 84-301 min), and median blood loss of 25 mL (range 5-100 mL). Enhanced 3-D visualization and increased mobility of surgical instruments provide surgeons with superior dexterity for performance of intricate movements required for the dissection of the lower esophageal sphincter. The most frequently reported postoperative symptom is reflux requiring pharmacologic management. The largest barrier for this procedure remains the high cost. Limitations to the knowledge of this procedure include the make-up of the literature being either case reports or retrospective studies. With the advent of POEM, the future role of RHM remains unclear, as patients often prefer a procedure that is perceived to be less invasive. Advantages of POEM compared to RHM is the absence of incisions and, in experienced hands, shorter operative time; on the other hand, RHM permits the addition of a fundoplication to mitigate reflux^[35]. The hospital length of stay and postoperative pain has been demonstrated to be similar between the two procedures^[36]. The advantages and disadvantages of RHM should be investigated with comparative studies and, ideally, randomized control trials.

DECLARATIONS

Authors' contributions

Performed literature review, contributed to manuscript writing: Sollie ZW

Contributed to manuscript writing: Jiwani AZ

Project oversight, author of techniques, contributed to manuscript writing: Wei B

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Multimodality imaging for preprocedural planning of percutaneous mitral valve repair: a comprehensive review

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Abstract

New transcatheter mitral valve (MV) therapies are now available as alternatives to surgical and medical treatments in patients at high or prohibitive operative risk. Multimodality imaging including echocardiography, cardiac magnetic resonance, and cardiac computed tomography provide complementary information to guide patient and device selection. Morphology and functional anatomy of the MV should be carefully evaluated to determine the feasibility of percutaneous treatment; to identify the best therapeutic approach, either leaflet or annulus or combined; and to predict the probability of procedural success that is crucial for subsequent outcome and should be integrated by comprehensive preprocedural assessment of chamber size, biventricular systolic and diastolic function, valvopathy hemodynamic impact and aortic or peripheral vascular disease. The spectrum of transcatheter options is now wide and encompasses leaflet repair, direct or indirect annuloplasty, and cordal implantation. The aim of this review is to provide an overview on the role of multimodality imaging in the patient selection and preprocedural planning of percutaneous mitral valve repair.

Keywords: Transcatheter mitral intervention; 3D-echocardiography; multimodality imaging



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INTRODUCTION

The burden of clinically significant mitral valve disease is noteworthy in the elderly population and therapeutic options were constrained due to patients' high operative risk so far. Thanks to new transcatheter mitral valve (MV) therapies, alternatives to surgical and medical treatments are now available. Accurate patient selection is crucial for procedural success and is based on careful preprocedural multimodality imaging evaluation. Echocardiography, cardiac magnetic resonance (CMR), and cardiac computed tomography (CT) may provide complementary information to guide patient and device selection. Evaluation of mitral valve anatomy, identification of MV lesion, and quantification of defect severity should be integrated by comprehensive preprocedural assessment of chamber size, biventricular systolic and diastolic function, hemodynamic impact, and aortic or peripheral vascular disease. The aim of this review is to provide an overview on the role of multimodality imaging in the patient selection and preprocedural planning of percutaneous mitral valve repair.

ECHOCARDIOGRAPHY

Echocardiography is pivotal for diagnosis, anatomical and functional characterization, and quantification of mitral regurgitation (MR) severity. Transthoracic echocardiography (TTE) is the first level imaging modality and allows a comprehensive evaluation of valve disease, chamber size, and function. Evaluation of mitral and pulmonary flow pattern as well as pulmonary artery pressure and chamber dimensions are precious indexes of hemodynamic load secondary to the valvopathy. Transesophageal echocardiography (TEE) is a second level imaging modality, and it is usually indicated for a deep evaluation of valve anatomy and MR grading. 2D echo allows both morphological and functional evaluation of the MV: the former is based on detection of leaflet abnormalities such as thickness, redundancy, and calcification, as well as identification of annular calcification, and the latter is based on evaluation of systo-diastolic leaflet motion according to Carpentier classification and is fundamental to understand the disease etiology and to guide the therapeutic strategy. 3D echocardiography (3DE) provides an added value in detailing MV morphology and precise localization of pathology through 3D rendering, multiplanar reconstruction (MPR), and 3D color-Doppler. 3D rendering is pivotal for morphological assessment as it provides a more realistic representation of the MV, which can be visualized through several perspectives^[1]. Moreover, 3DE is superior to 2D echo in detailing the lesions in terms of scallop disease and commissural involvement^[2] and localizing the calcifications and additional findings such as clefts or tissue deficiency. The MPR mode allows the assessment of annular dimensions and its dynamics during the cardiac cycle^[3], mitral valve area (MVA), and characterization of the disease (flail/prolapse detection, localization, and analysis) [Figure 1]. Furthermore, it allows studying specific sites of interest such as the potential grasping zone for transcatheter repair with leaflet approach in terms of measurement of posterior leaflet length, leaflet motion, and calcification/thickness [Figure 2].

The site of origin of the regurgitant jet may be identified by 3D color-Doppler, especially from the left ventricular perspective that directly shows the flow convergence area. Moreover, measurement of 3D vena contracta area is a new method for MR quantification showing higher accuracy compared to 2D color-Doppler, particularly in the presence of multiple or eccentric MR jets^[4]. Color-coded 3D parametric maps may be created by either automatic or semiautomatic software, provide indices of MV remodeling, and may localize MV pathology^[5].

Finally, 3D transthoracic echo provides reproducible measurement of LV volumes and function with similar accuracy compared to CMR^[6].

Speckle tracking imaging represents a more sensitive tool to assess LV dysfunction than ejection fraction and may improve the selection of candidates for the procedure. Recently, baseline GLS value <-9% has been

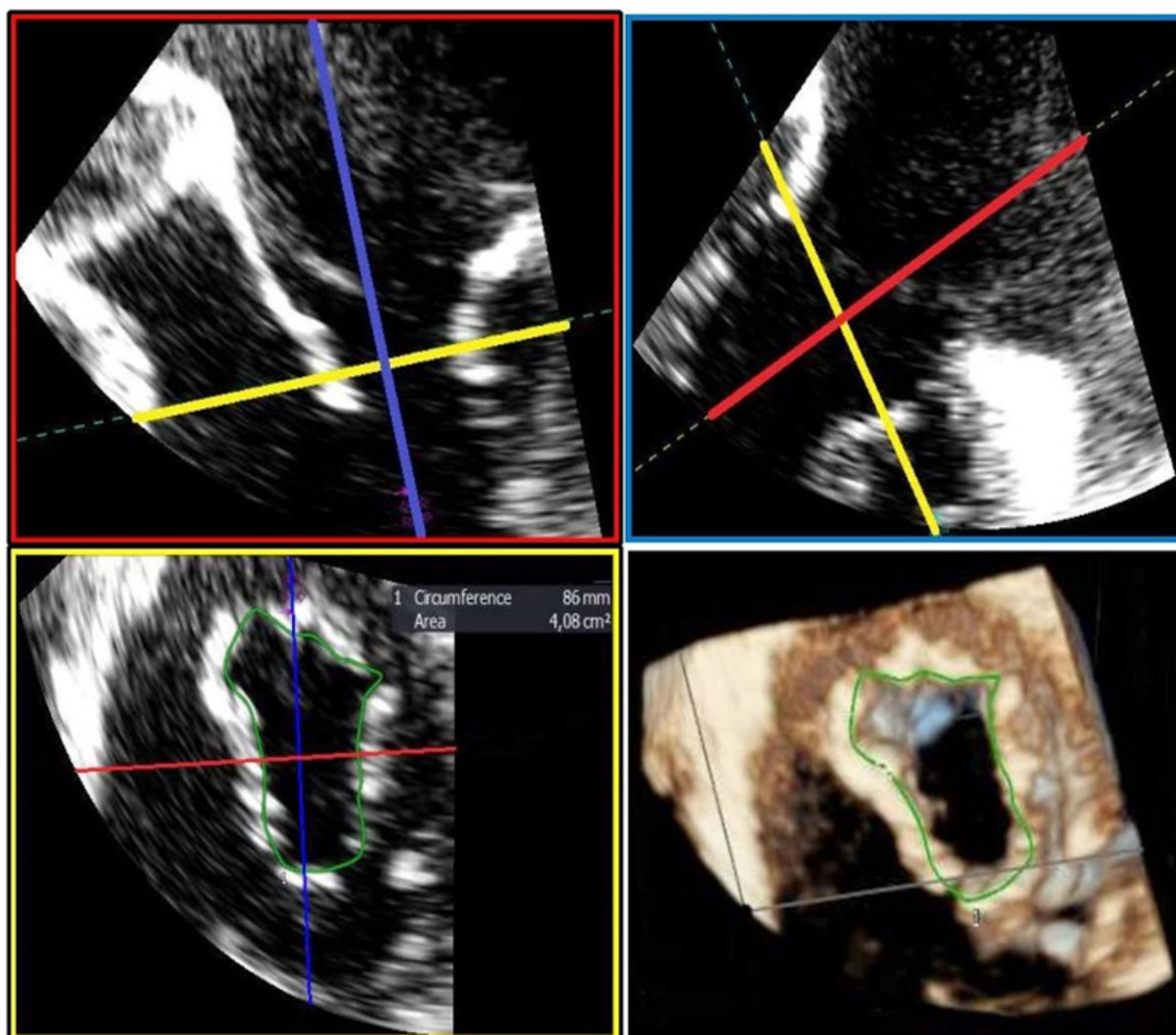


Figure 1. MPR analysis of 3D dataset to measure mitral valve area. The mitral valve is fully open. The tips of mitral leaflets are identified in the blue and red planes to delineate the orifice, allowing the measurement of the mitral valve area on the axial. MPR : multiplanar reconstruction

demonstrated to be an independent predictor of LV reverse remodeling and clinical outcomes in patients with secondary MR treated with MitraClip^[7].

Preprocedural evaluation of MR severity should be performed according to EACVI and ASE guidelines for native valve regurgitation^[8,9]. Different methods are available such as qualitative (visualization of color-Doppler regurgitant jet area and evaluation of continuous wave Doppler signal), semi-quantitative (vena contracta width, mitral inflow velocity, and pulmonary vein flow pattern), or quantitative (effective regurgitant orifice area (EROA), regurgitant volume (RVol), and regurgitant fraction (RF) by PISA or volumetric method). As a true gold standard for accurate MR grading is not available, a multiparametric approach is the cornerstone for a reliable quantification of MR. Qualitative and quantitative parameters have different strengths and weaknesses that should be balanced to reduce their own limitations: jet area is linearly correlated with the driving pressure and may underestimate eccentric jets; vena contracta width measurement assumes the EROA to be circular; pulsed wave Doppler analysis of mitral and pulmonary flow is highly dependent on intra-chambers pressures and left atrial compliance; and PISA method is affected by time of regurgitation and shape of flow convergence area^[9]. The quantitative assessment of

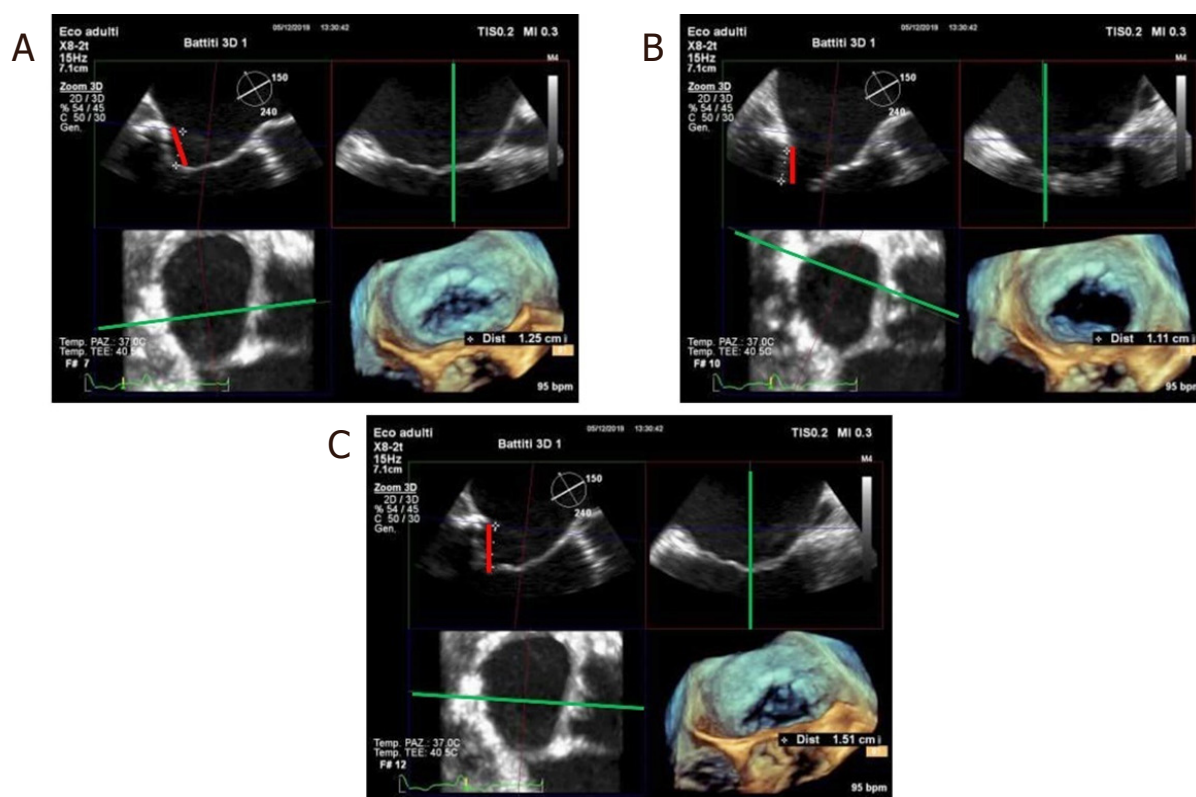


Figure 2. Usefulness of MPR method to measure the posterior leaflet length in specific area of interest identified by the green plane: (A) centro-lateral; (B) central; and (C) centro-medial. MPR : multiplanar reconstruction

secondary MR is further affected by the following conditions: the regurgitant orifice is often crescent-shaped, the proximal convergence zone is irregular, jets could be multiple and eccentric, often shows a typical biphasic pattern, and systolic blunting of the pulmonary venous flow pattern may be influenced by the underlying cardiomyopathy.

The analysis of 3D vena contracta area (3D VCA) can overcome the geometric assumptions of 2D PISA method, and it has shown a good correlation with regurgitant volume calculated by CMR [Figure 3]. Moreover, the ability to correctly localize jets makes the 3D-VCA very useful when multiple MR jets are present and the measurement of EROA or VC from a single jet does not reflect the true regurgitant volume^[10]. However, the optimal cut-off value of 3D VCA to define severe MR is still debated.

Finally, a careful evaluation of LV volumes, EF, and effective stroke volume is essential. Ventricles of different volumes can have similar EROAs but different RVol and RF. ASE and EACVI guidelines consider different thresholds to discriminate severe MR. An algorithm for quantitative assessment of FMR based on estimation of RF has been proposed to further stratify the patients among those within the grey area (EROA of 20-30 mm² and a RVol of 30-44 mL), identifying patients with RF > 50% those at high risk^[11].

Stress echocardiography may represent an added value in patients presenting with discordant symptoms and rest echocardiography, allowing to evaluate effort tolerance and variation in regurgitant volume during exercise^[1]. Experience on stress echo in the setting of percutaneous mitral valve repair is still limited and most evidence derives from studies on patients undergoing MV surgery: an exercise induced systolic pulmonary artery pressure (sPAP) > 60 mmHg, exercise induced right ventricular dysfunction, and a reduced LV contractile reserve (exercise increase in ejection fraction < 4% or increase in global longitudinal

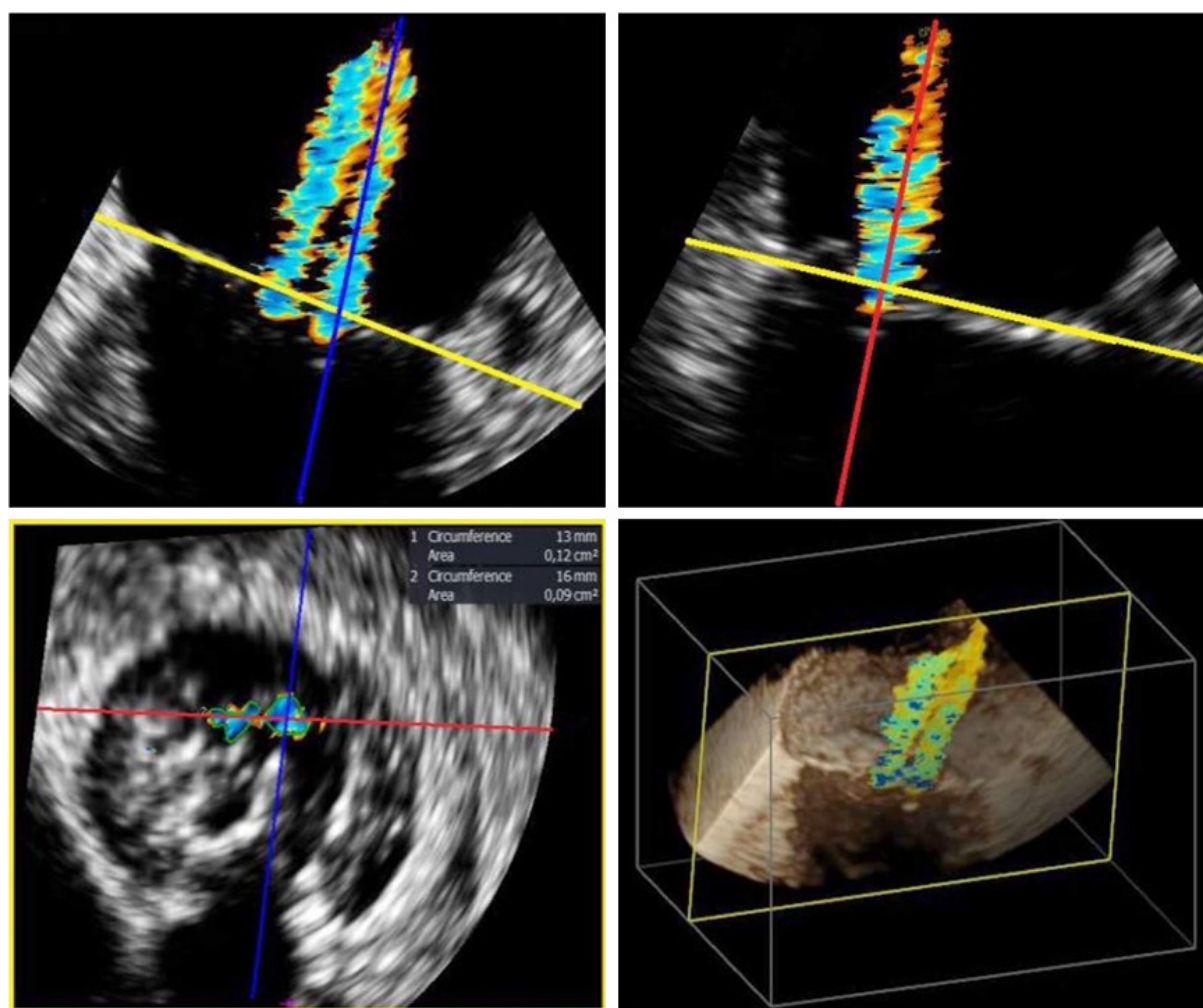


Figure 3. MPR reconstruction of the regurgitant jet. The narrowest portion of the jet close to the tip of the leaflets is identified and vena contracta area is measured on the axial plane (yellow). The measurement may be done for each regurgitant jet and the value. MPR: multiplanar reconstruction

strain < 2%) have been identified as predictors of poor prognosis in degenerative MR^[1]. In secondary MR, an exercise increase in EROA > 0.13 cm² and sPAP > 60 mmHg carry a poor prognosis^[12], while MR decrease with exercise because of improvement of walls motion, recruitment of ischemic segments, and ultimately reduction of the tethering forces could identify patients who would benefit from optimal medical therapy and revascularization prior to the correction of mitral disease^[13]. On this basis, a study on 39 patients treated with MitraClip confirmed that a decrease in MR grade during stress echo was associated with limited clinical benefit from the procedure^[14].

CARDIAC MAGNETIC RESONANCE

CMR is the gold standard to assess cardiac dimension, function, and tissue characterization. It has acquired an emerging role in the context of MV as a reliable quantitative method to assess MR in discordant cases or when echocardiography is of poor quality. It can provide an effective quantification of MR, also in the context of multivalvular disease, without limitations of imaging window or body habitus. The measurement of the Rvol requires two different imaging techniques: steady state free precession (SSFP) sequences to calculate left ventricular (LV) stroke volume from the difference between LV diastolic and systolic volumes and phase contrast sequences to measure the LV forward stroke volume^[15] [Figure 4]. RVol and RF are calculated as difference between LV total stroke volume and forward flow.

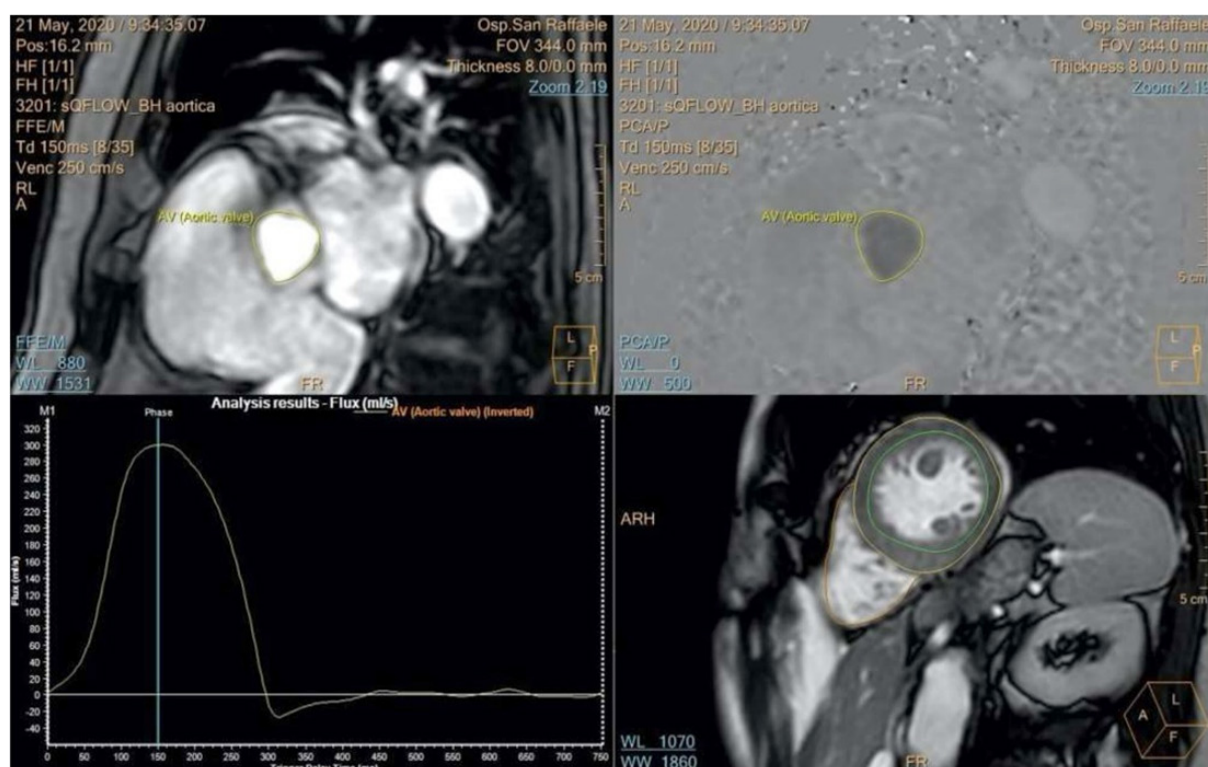


Figure 4. Quantification of mitral regurgitation by CMR. SSFP sequences to evaluate LV stroke volume from the difference between LV diastolic and systolic volumes (bottom right) and phase contrast sequences to measure the LV forward stroke volume (top). CMR: cardiac magnetic resonance; SSFP: steady-state free precession imaging; LV: left ventricle

The limits of CMR include the duration of the exam, the difficulties in identifying correctly the basal slice of LV in SSFP sequences, and the need to select the correct perpendicular slice to the ascending aorta with the correct velocity encoding setting in phase contrast sequences.

CMR was firstly compared to angiography with good correlation, however existing discordances in the assessment of regurgitation with transthoracic (TT) and transesophageal (TE) 2D/3D echocardiography remain even in presence of severe regurgitation^[15,16]. In five studies^[17-21], the agreement between CMR and 2D echocardiography among patients diagnosed with severe regurgitation ranged between 20% and 66%, with echocardiography usually showing more severe regurgitation than CMR. Studies comparing CMR with 3D echocardiography reported improved absolute agreement, but with wide limits of agreement, suggesting that the grading differences remain^[22,23].

In the upcoming years, the potential advancement of the 4D-flow CMR retrospective valve tracking method, quantifying flow directly at mitral valve, could further improve CMR assessment^[24].

The thresholds that define severity in CMR might differ from echocardiography since the latter seems to quantify a larger RVol in the same patient^[25] and the actual recognized cut-offs for CMR are RVol > 55-60 mL and RF > 40%^[17,26,27].

Limited data are available comparing CMR and echo for detection of leaflet abnormalities.

A fundamental added value of CMR is considered the ability to accurately evaluate cardiac chamber function and dimensions^[9] and to characterize the extent of scarring and myocardial viability, which

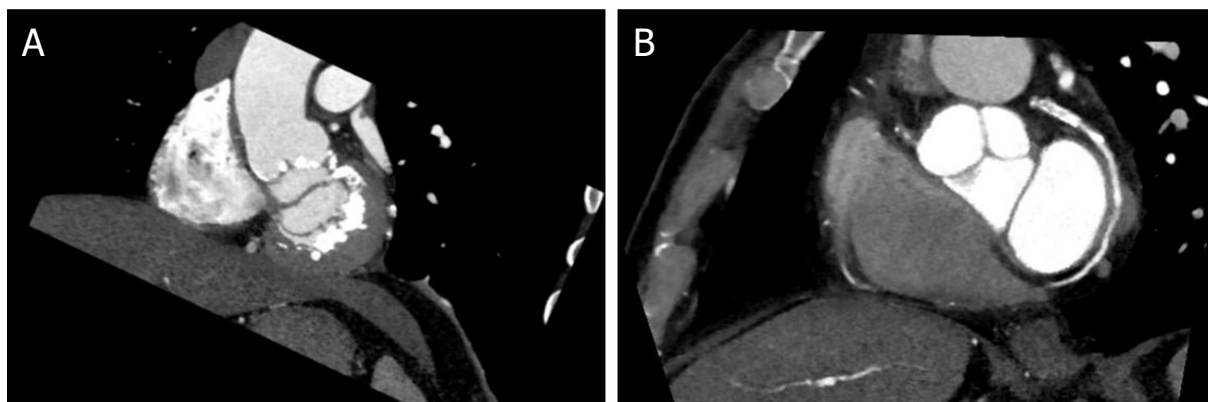


Figure 5. (A) Cardiac CT short-axis view of the mitral valve at the level of the mitral annulus, showing annular calcification; and (B) short axis view at the level of the atrioventricular groove showing the course of the left circumflex artery

provides further stratification over ventricular volumes^[28]. In degenerative mitral valve prolapse, it allows easy detection and quantification of the mitral annular disjunction and assessment of LV posterior wall and papillary muscle fibrosis for arrhythmic risk stratification^[29,30].

Finally, CMR is useful to assess structural abnormalities of the MV apparatus, such as anomalous insertion of papillary muscle directly into the AML or hypertrophied and apically displaced anterolateral papillary muscle in hypertrophic cardiomyopathy^[31].

COMPUTED TOMOGRAPHY

Cardiac multidetector computed tomography (MDCT) has an excellent spatial resolution and is highly reproducible, being relatively operator-independent. On the other hand, the temporal resolution is inferior compared to echocardiography and MRI, and the quality of the exam is highly dependent on the arrhythmic burden. The technical suggestion for optimal analysis of MV apparatus is the retrospective ECG-gated acquisition of R-R interval from 0% to 90%, in order to have all the datasets available for MPR and correction of arrhythmia-related artifacts. Moreover, to limit the artifacts and increase the temporal resolution, a CT scanner with 64 detector rows is recommended^[32]. MDCT, thanks to its excellent blood-tissue interface and the high-spatial 3D imaging, provides a comprehensive visualization of cardiac and vascular structures and can give detailed information on mitral annular shape and sizing, valvular calcification, papillary muscles position and dimension, LV shape and dimension, and the relationship of the heart with chest wall. Furthermore, multiplanar and curved planar (CPR) reconstructions allow a comprehensive assessment of the course of coronary arteries and veins with respect to MV apparatus^[33].

MDCT is the gold standard for the precise location, extension, and objective quantification of calcifications [Figure 5]. The extent of calcifications into the annulus (MAC), the leaflets, and the subvalvular apparatus, as well as in the myocardium and left ventricle outflow tract, can be easily visualized. Finally, MDCT may play an emerging role in MV valve evaluation to determine MV area^[34], leaflet length, prolapse/flail parameters, tethering angles, and quantification of MR^[35].

CHOICE OF TRANSCATHETER MITRAL VALVE REPAIR APPROACH

Patients with significant mitral regurgitation may present comorbidities or technical challenges that increase surgical risk or contraindicate surgery. These patients, if symptomatic or requiring recurrent hospital admission for heart failure despite optimal guideline-directed medical therapy, represent candidates to percutaneous interventions. However, morphology and functional anatomy of the mitral valve should be

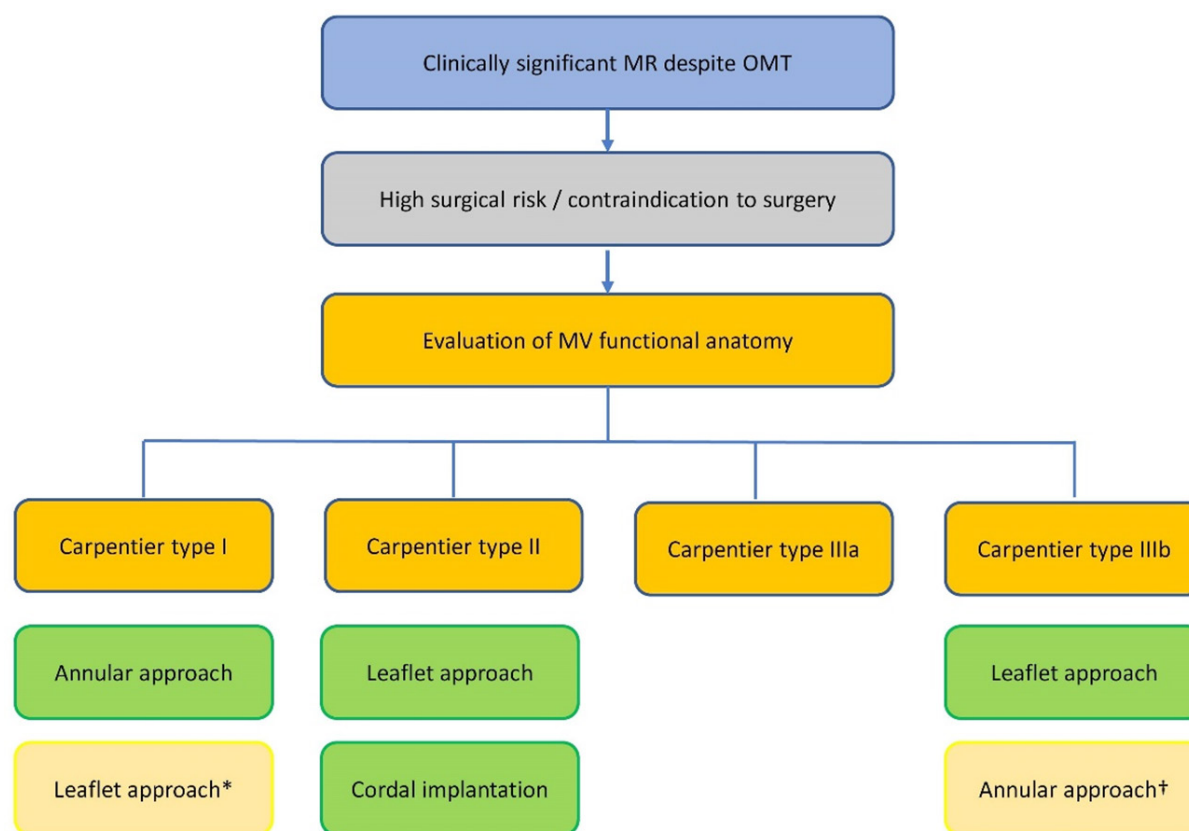


Figure 6. Spectrum of available transcatheter mitral valve repair options according to functional anatomy of the mitral valve. *Expected suboptimal result due to residual annular dilatation; † ideal tethering should be limited (coaptation depth < 10 mm)

carefully evaluated to determine the feasibility of percutaneous treatment; to identify the best therapeutic approach, either leaflet or annulus or combined; and to predict the probability of procedural success that is crucial for subsequent outcome.

Both primary and secondary MR may be treated with a leaflet approach, while the annular approach is usually reserved for secondary MR. Functional classification helps to understand pathology and further guide therapeutic approach [Figure 6]: Carpentier Type I, normal leaflet motion and position (annular dilation, leaflet perforation, cleft); Type II, excess leaflet motion (prolapse, flail); Type IIIa, restricted leaflet motion in systole and diastole (rheumatic, fibro-calcification); and Type IIIb, restricted leaflet motion in systole (tethering secondary to ischemic or non-ischemic cardiomyopathy). In absence of specific contraindications, a leaflet approach is suitable for treating Types II and IIIb and suboptimal for Type I, while annular approach is most appropriate for Types I and IIIb if limited leaflet tethering is present.

PREPROCEDURAL PLANNING FOR TRANSCATHETER MITRAL LEAFLET REPAIR

Transcatheter leaflet repair is based on the surgical technique developed by Alfieri^[36]. Two devices (MitraClip, Abbott, Illinois, USA; and PASCAL, Edwards Lifescience, California, USA) that allow reproducing the technique into a catheter-based approach are available thus far. The devices are equipped with two arms to grasp and approximate the free edges of anterior and posterior mitral leaflets.

The site origin of the jet represents the target lesion, so a preprocedural evaluation is firstly aimed at evaluating leaflet tissue quality, length, and mobility in the area of potential grasping zone. The analysis of the 3D dataset by MPR represents an added value for this purpose, allowing the evaluation of leaflet

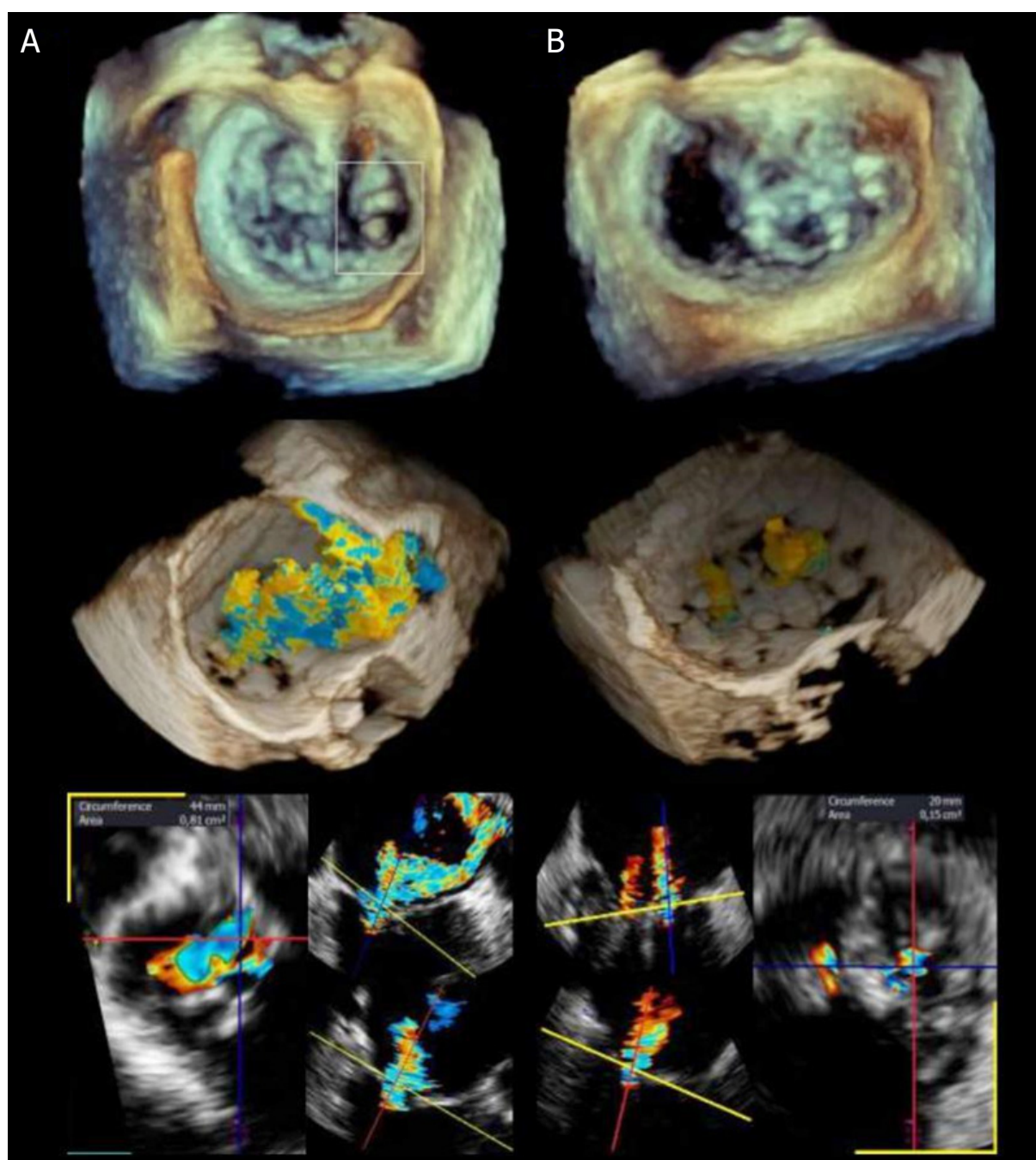


Figure 7. Challenging mitral valve anatomy for percutaneous repair with leaflet approach: commissural large eccentric regurgitant jet originating from P3 prolapse (Column A) effectively treated with the implantation of three clips (Column B)

thickness, calcification, mobility, and measurements in the area of interest [Figure 2]. 3D color-Doppler, especially when using the ventricular perspective, is superior to 2D color-Doppler to localize the jet with greatest flow convergence area. Measurement of MVA by MPR analysis of 3D dataset is a fundamental step of preprocedural evaluation to avoid significant stenosis after the procedure.

Nowadays, challenging MV anatomies [Figure 7] may be approached in tertiary care centers that recognize only the following as absolute contraindications: a mitral valve area $< 3 \text{ cm}^2$, calcification in the potential grasping zone [Figure 8A], large cleft extending to the hinge point [Figure 8B], very short PML ($< 7 \text{ mm}$),

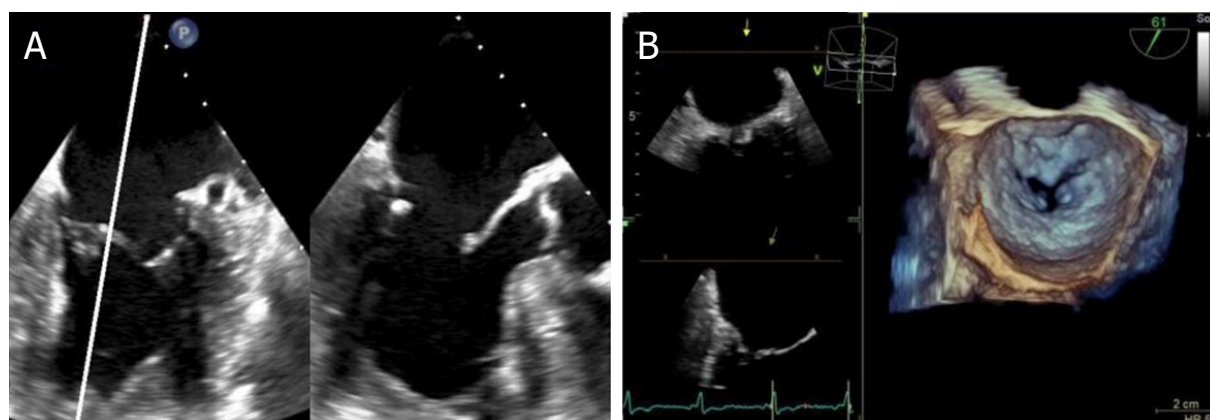


Figure 8. Unsuitable mitral valve anatomy for percutaneous repair with leaflet approach: (A) simultaneous biplane image showing calcification of posterior leaflet in the potential grasping zone; and (B) 3D volume rendering of the mitral valve showing large cleft extending to the hinge point of the posterior leaflet

Table 1. Challenging morphological criteria for percutaneous MV repair

MVA between 3-4 cm ²
PML length between 7-10 mm
Commissural pathology
Small cleft
Presence of calcification outside the grasping zone
Small fossa ovalis
Previous MV plasty

MVA: mitral valve area; PML: posterior mitral leaflet; MV: mitral valve

and endocarditic/rheumatic etiologies or multiple lesions in the context of Barlow disease. Suboptimal MV morphological criteria for performing the procedure are detailed in [Table 1](#). Use of PASCAL (Edwards Lifesciences, USA), thanks to its structural central spacer, may represent a therapeutic option in challenging anatomies (large malcoaptation area, severe annular dilatation, large flail, or prolapse gaps).

The 3D rendering makes easier the identification of cleft-like indentations, congenital clefts, commissural gaps, and perforations that may represent contraindications to the procedure, but emerging experiences in this setting are promising^[37].

Accurate description of the interatrial septum should be performed as the procedure requires a site-specific transseptal puncture in the postero-superior part of the fossa ovalis, 4-4.5 cm above the MV annulus. Indeed, the presence of a patent foramen ovale, a “floppy” septum, and a small fossa ovalis (FOV) predicts a challenging trans-septal puncture.

For degenerative mitral valve prolapse/flail, the number and identification of diseased segments should be evaluated. The analysis of 3D volumes by MPR can precisely localize [\[Figure 9\]](#) and provide measurement of extension of prolapse/flail (flail gap and flail width, respectively, are ideally < 10 mm and < 15 mm; a flail width > 10 mm or high flail gap may predict the need for multiple clips) and discriminate primary and secondary lesion, with the latter possibly left untreated if the principal lesion has been effectively addressed.

In the context of secondary MR, the degree of restriction of posterior leaflet and the degree and extension of coaptation gap (loss of systolic leaflet coaptation in the target zone, easily assessed by 3D en-face view from LA) should be systematically evaluated. Extension of MV remodeling may be quantified through

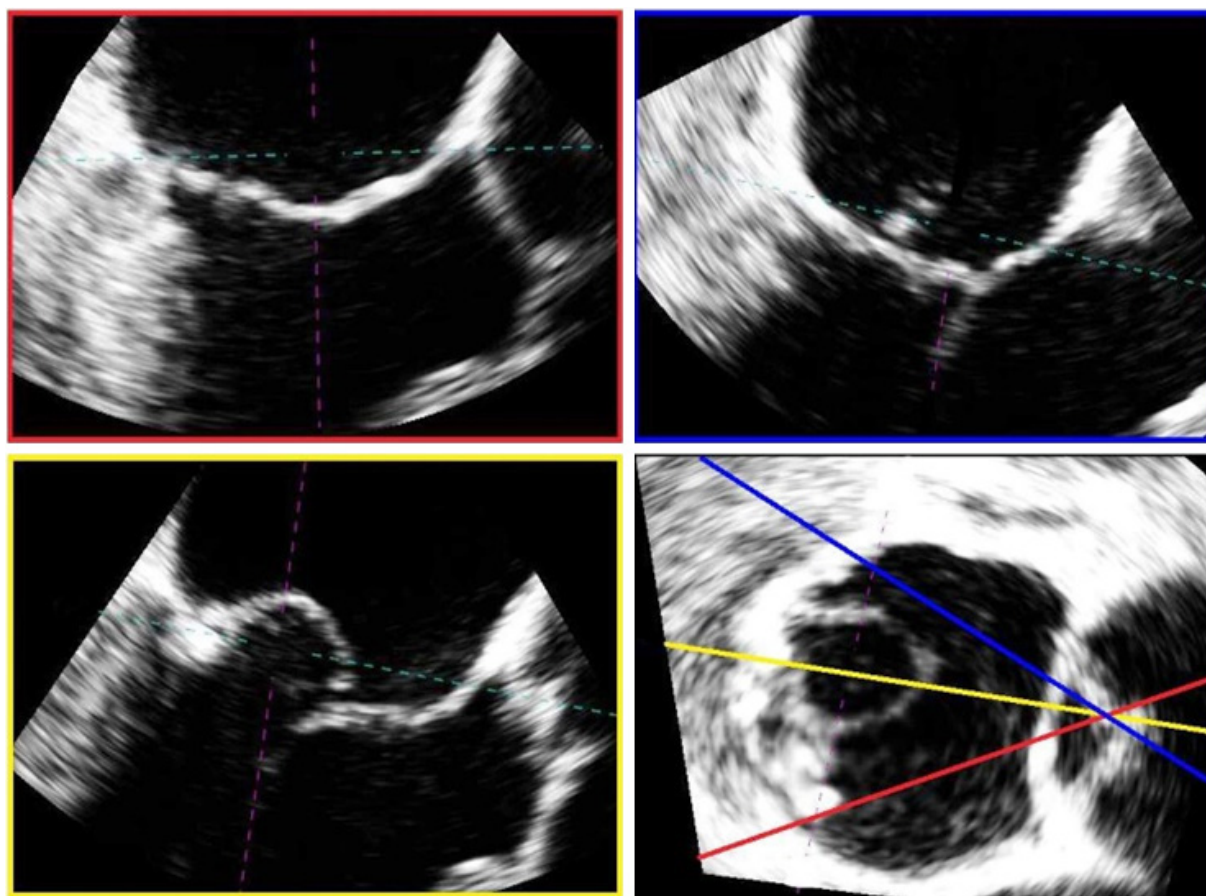


Figure 9. Multiplanar reconstruction analysis of 3D dataset clearly localizing prolapse of the P2 segment and showing preserved leaflet coaptation in commissural segments

measurement of coaptation depth (distance from the annular plane and the coaptation point, index of tethering) and coaptation length (index of coaptation reserve) that may be assessed in the potential grasping zone by MPR or derived from parametric color-coded maps. Moreover, as contemporary trials have shown, the decision to clip cannot be drawn before a comprehensive evaluation of ventricular dimension and function. Although a unifying, widely accepted explanation for contrasting results of MITRA-FR and COAPT trials has not yet been identified, corroborating evidence suggesting a lack of benefit from the procedure in patients with advanced heart failure is emerging: extreme left ventricular dilation and dysfunction^[38,39] and right ventricular dysfunction^[40] have been identified as predictors of poor prognosis. The complex interplay between LV geometry and mitral valve function should be taken into account during evaluation for mitral intervention, and EROA/LV end diastolic volume ratio has been proposed to translate it into a measurable variable in order to discriminate patients with features of proportionate or disproportionate MR, with only the latter having survival benefit from the procedure^[41]. However, concerns on this hypothesis have been raised, relying on accuracy of volume measurements in COAPT trial^[42] and highlighting the need for further studies with reliable quantitative measurements for MR and LV volumes by comprehensive multimodality imaging.

PREPROCEDURAL PLANNING FOR MITRAL VALVE ANNULOPLASTY

The rationale of surgical annular ring reduction in secondary MR is to improve leaflet apposition, and hence the coaptation reserve, and to prevent the further annular dilatation, without disrupting the mobility of the leaflets. This is achieved through the anterior translation of the posterior annulus, reducing the

Table 2. Predictors of recurrent MR after isolated surgical MV undersized annuloplasty

Left ventricular end-diastolic diameter > 65 mm
Distal anterior mitral leaflet angle > 25°
Posterior mitral leaflet angle > 45°
Systolic tenting area > 2.5 cm ²
End-systolic interpapillary muscle distance > 20 mm
Systolic sphericity index > 0.7
Coaptation depth > 10 mm

MV: mitral valve; MR: mitral regurgitation

antero-posterior diameter either directly using the Cardioband (Edwards Lifesciences, California, USA) or indirectly with the Carillon device (Cardiac Dimensions, Washington, USA). Secondary MR responsive to annular reduction, according to Carpentier's classification, are Type I (incomplete coaptation due to annular dilatation/deformation, mainly secondary to AF and diastolic dysfunction) and Type IIIb (leaflet tethering with low degree of MV remodeling).

Severe MAC is a contraindication for direct and indirect mitral annuloplasty since it impedes optimal anchoring and contracting of the devices. Surgical experience clearly provides predictors of recurrent MR after isolated undersized annuloplasty^[43] [Table 2]. Thus, patient selection is crucial, with ideal candidates being patients with limited leaflet tethering, as suggested by high rate of recurrent MR observed in randomized trials in surgically unselected series^[44].

Mitral annulus anatomy as well as relationship with circumflex artery and coronary sinus should be evaluated to assess procedural feasibility and predict procedural success and complications, taking into account the high anatomical variability^[45].

The preprocedural planning for direct annuloplasty includes the measurement of the circumference of the posterior MA (from the left to right trigones) at maximum opening of the MV as well as MA area, antero-posterior and medio-lateral diameters, and sphericity index (antero-posterior/mediolateral diameters ratio) obtained preferably by MDCT. MA may also be assessed using echocardiographic 3D dataset by MPR or with dedicated software. The annular thickening should also be measured (minimum desired value is 4 mm). MDCT is fundamental to assess the presence, degree, and localization of calcium in the annulus and its extension to the myocardium or leaflet. Noble structures with close relationship with the MA should always be evaluated during the preprocedural planning with dedicated reconstruction by MDCT such as the left circumflex artery (LCX) [Figure 5B], the coronary sinus, and the non-coronary and left coronary aortic cusps adjacent to the base of the anterior leaflet. A minimum distance of 2.5 mm from the patch of the anchor to the LCX is required to avoid lesion of the artery. Dedicated software based on MDCT can provide the expected intraprocedural fluoroscopic projections and the 3D preview of the final system position^[32,46].

The preprocedural planning of indirect mitral annuloplasty via the coronary sinus requires additional anatomical considerations [Figure 10]. Patency, diameter, tortuosity of the coronary venous system, location and extent of the Thebesian and Vieussens valves, and the spatial relationship of the coronary sinus with respect to the MA and LCX should be evaluated prior the procedure. Distance between the LCX and the coronary sinus must be measured to avoid the coronary impingement during traction of the device. Moreover, to ensure a correct transmission of tension to the annulus, the coronary sinus and MA should lie on the same horizontal plane, information easily obtained by MPR of MDCT dataset. It is quite common for the CS to be located superior to the MA level, thus leading to suboptimal annuloplasty result, because the chincing effect will affect the left atrial wall^[47].

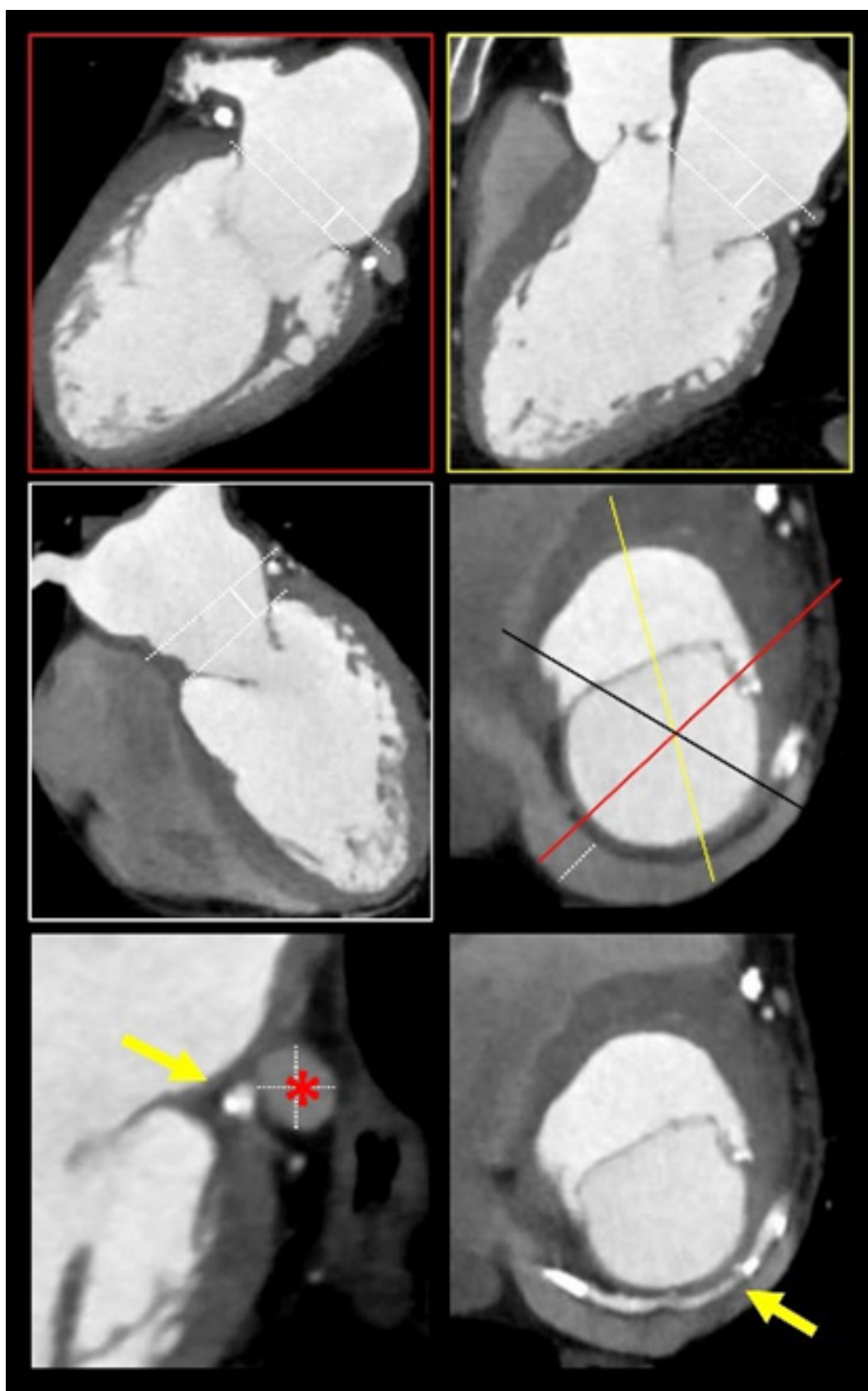


Figure 10. CT preprocedural planning for indirect annuloplasty showing spatial relationship of the coronary sinus with respect to the mitral annulus plane and the LCX (yellow arrow) and CS (red asterisk). LCX: left circumflex artery; CS: coronary sinus

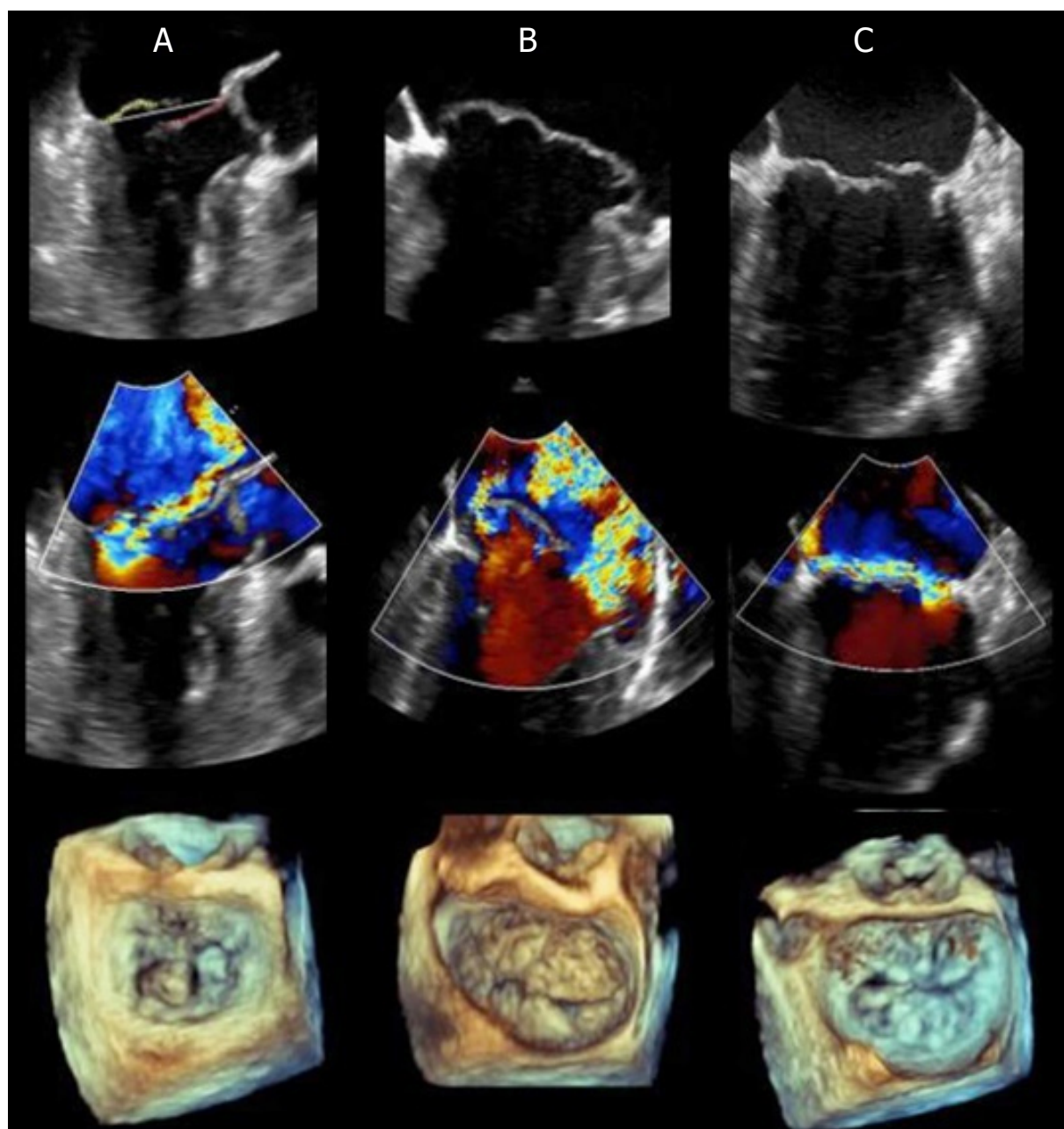


Figure 11. Favorable MV anatomy for chordal implantation: isolated P2 prolapse (A). Unfavorable MV anatomy: (B) bileaflet multiscallop prolapse; and (C) commissural prolapse. MV: mitral valve

Among imaging modalities, invasive venography is the gold standard for the assessment of coronary sinus anatomy; moreover, simultaneous coronary angiography allows assessment of the relation with the coronary arterial tree^[48].

PREPROCEDURAL PLANNING FOR MITRAL CHORDAL IMPLANTATION

Transapical chordal implantation using the NeoChord DS1000 system (NeoChord, Inc., Minnesota, USA) or Harpoon (Edwards Lifescience, California, USA) is a minimally invasive MV repair procedure addressing the correction of isolated prolapse or flail of the posterior leaflet in patients without significant annular dilatation^[49]. The aims of the preprocedural assessment are: (1) ascertain that patients meet some

strict anatomical criteria (isolated prolapsed/flail of P2 with a central regurgitant jet); (2) absence of significant annular dilatation; (3) adequate length of the posterior leaflet compared to the antero-posterior MA diameter (ideally > 21%); (4) adequate coaptation leaflet reserve; (5) evaluation of MAC because this may cause shadowing and impaired visualization of the device; and (6) determination of the transapical access^[50-52] [Figure 11].

Transthoracic echocardiography is frequently used to decide the optimal intercostal space and location for the mini-thoracotomy. MDCT permits the visualization of the anatomical relation between apex and chest wall and the definition of a trajectory for the device.

CONCLUSION

Transcatheter mitral valve interventions provide a new spectrum of therapeutic options for high-risk patients. Accurate patient selection and choice of the treatment strategy, either leaflet or annular approach, or combined, goes through a comprehensive preprocedural multimodality imaging evaluation aimed at the characterization of the functional anatomy of MR and its interplay with left ventricular geometry and function.

DECLARATIONS

Authors' contributions

Proof writing: Melillo F, Boccellino A

Proof revision: Ingallina G, Ancona F, Capogrosso C, Napolano A, Stella S, Agricola E

Conception and design: Melillo F, Agricola E

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Technical Note

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Minimizing complications after minimally invasive surgery for epiphrenic diverticula of the esophagus: technical tips

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Abstract

Epiphrenic diverticula occur within the distal 10 cm of the esophagus. Because they are secondary to an underlying esophageal motility disorder, the surgical treatment of these diverticula must include a myotomy in addition to the resection of the diverticulum. In selected cases, the diverticulum can be left in place, performing only the myotomy and the partial fundoplication. Most patients will eventually become asymptomatic and the diverticulum can be left in place. Overall, it is a challenging operation that may be associated to significant morbidity. In this review, we illustrate the key technical elements and how to troubleshoot eventual problems.

Keywords: Esophageal epiphrenic diverticulum, high resolution manometry, esophageal motility disorders, achalasia, diverticulectomy, esophageal myotomy

INTRODUCTION

Esophageal diverticula are an uncommon disorder with an incidence less than 4% in endoscopic and radiologic series^[1]. They are located above the sphincters that delimit the esophagus (epiphrenic diverticulum for the lower esophageal sphincter and Zenker's diverticulum for the upper esophageal sphincter) and are secondary to dysfunction of these sphincters. This leads to increased pressure and herniation of the mucosa through gaps in the muscular layer (pulsion pseudodiverticulum) or in the



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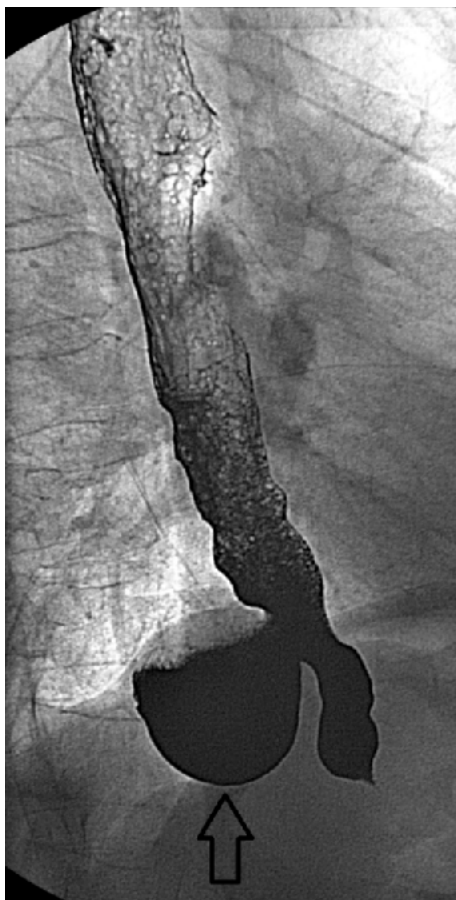


Figure 1. Barium esophagram disclosing an epiphrenic diverticulum (arrow)

esophageal body (Rokitansky diverticulum), classically linked to the tuberculosis era when inflamed mediastinal lymph nodes were believed to create adhesions to the esophageal wall (true traction diverticulum)^[2], although recent studies also showed the role of dysmotility in the genesis of these diverticula^[3].

Zenker's diverticulum is located in the area of the upper esophageal sphincter and treated by either an open cervical or an endoscopic approach^[1]. Midthoracic diverticula are usually asymptomatic^[3] and represent only 15% of the esophageal diverticula^[4]. Intramural pseudodiverticulosis is a rare condition mostly linked to the mucosa^[5]. These conditions are not treated here.

Epiphrenic diverticulum (ED) [Figure 1] occurs within the distal 10 cm of the esophagus^[2]. It is associated to esophageal dysmotility^[6]. The most common named esophageal motility disorder linked to this disease is achalasia^[7]. ED is usually treated by a minimally invasive approach, but some series show suboptimal outcomes with up to 23% leak rate and 20% need for a reoperation^[8]. In this series dedicated to Postoperative Complications and Recovery of Minimally Invasive Esophageal Surgery, we may propose three points for discussion as technical tips to improve outcomes and minimize complications in the treatment of ED: conservative approach in selected cases, the abdominal approach when surgical therapy is indicated, and the isolated treatment of the esophageal dysmotility without diverticulectomy.

ABDOMINAL APPROACH

Most authors advocate the surgical treatment for ED with a cardiomyotomy (Heller's operation) and diverticulectomy^[8-10]. This form of treatment was historically performed through a thoracotomy. In the

era of minimally invasive surgery, thoracoscopy replaced thoracotomy as the preferred approach^[9]. The thoracic approach gained popularity due to easy access to the diverticulum, especially in situations when its ostium is more proximal into the esophagus. The thoracic route has some disadvantages as compared to the abdominal approach that goes farther than the pulmonary morbidity and pain. The myotomy is associated to worse outcomes when performed through the chest as compared to the abdominal route, especially due to a high rate of gastroesophageal reflux^[11]. In addition, the development of staplers made easier the resection of the diverticulum via laparoscopy^[9]. These advantages shifted the preference of modern authors to the laparoscopic route^[8]. In addition, the laparoscopic approach allowed the performance of a partial fundoplication after the myotomy to prevent pathologic reflux.

When outcomes are compared, disease recurrence is rare for both approaches^[8] and the results seem to be similar for thoracoscopy and laparoscopy^[8,12-14]. If diverticulectomy is considered important (due to symptoms) after a laparoscopic myotomy and partial fundoplication, a thoracoscopic diverticulectomy is safer.

Some technical tips may result in better outcomes^[10]. First, dissection of the upper border of the diverticulum and of its neck is the most challenging aspect of the laparoscopic route. Even though the diverticulum may appear to be located high in the esophagus, dissection of adhesions to surrounding tissues and sufficient traction of the diverticulum and esophagus with a Penrose drain circling the esophagogastric junction frequently allows dissection of high diverticula from below. It is important to dissect the neck of the diverticulum free of the surrounding tissue and to clearly identify the muscle layers. It must be remembered that ED is pseudodiverticulum, thus muscular fibers cannot be found at the diverticulum itself. Some authors add an extra port for further assistance^[15].

If the diverticulum will be resected, it is better performed on the opposite side of the diverticulum to avoid interference with the resection and the muscle closure at that site. If the diverticulum will not be resected, myotomy can be performed at the level of the neck of the diverticulum and extend onto the gastric wall as in a Heller myotomy for achalasia. For the diverticulectomy, a 50-56-F bougie is placed inside the esophagus to avoid narrowing of the lumen when the stapler is applied. Reticulating staplers should be preferentially used to facilitate optimal positioning across the neck of the diverticulum, and the staple height should be appropriate for the thickness of the tissue at the transection site. The muscle layers should be approximated over the staple line with interrupted stitches. A partial fundoplication completes the procedure [Figure 2].

Treatment of the dysmotility without diverticulectomy

An esophageal motor disorder is present in the majority, if not in all, patients with ED^[6,10]. A cardiomyotomy is always necessary when treating a symptomatic diverticulum, even if a dysmotility was not detected by esophageal manometry because: (1) an esophageal dysmotility may not be detected by conventional parameters and be missed by unexperienced physiologists^[6]; (2) esophageal dysmotility such as achalasia rather than the diverticulum per se may be responsible for most of the symptoms, such as dysphagia and pulmonary symptoms^[10,16]; and (3) the addition of a myotomy decreases the chance of leak due to a lower intraluminal pressure^[17].

A recent systematic review and meta-analysis with 511 patients^[14] showed that the diverticulum was left in situ in only 7% of the cases, mostly due to small size. Castrucci *et al.*^[18] also did not perform a diverticulectomy in the presence of wide-necked diverticula without food retention in the pouch, pulmonary aspiration, or mucosal lesions. D'Journo *et al.*^[19] advocated suspension of wide-necked diverticula when there is no dependent portion of the diverticular sac and myotomy alone in the presence of multiple small diverticula. Interestingly, outcomes were similar when the diverticula were resected or left in place.

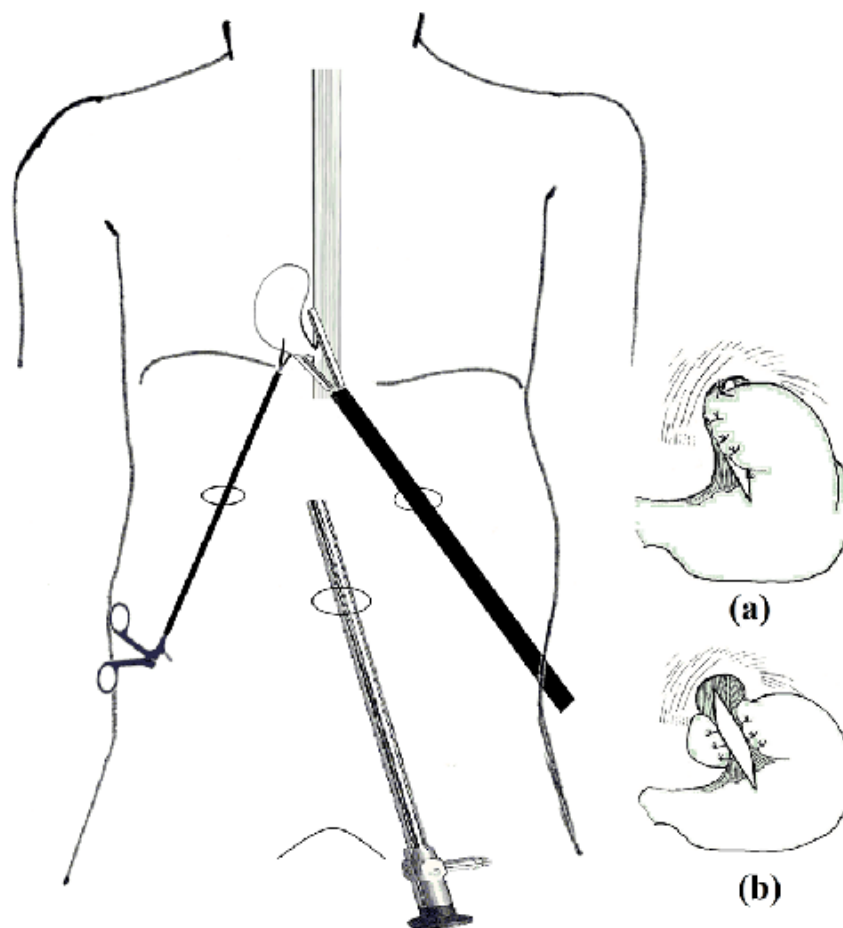


Figure 2. Laparoscopic resection of epiphrenic diverticulum (left). The operation also includes a myotomy and partial fundoplication, either a Dor (a) or Toupet (b). Reproduced from Reference^[1] with permission by Springer

Allaix *et al.*^[20] compared the outcomes for resected *versus* non-resected diverticula in a multicenter study. Among 13 patients, in seven the diverticulum was not excised. The reasons for this approach were small size or technical reasons (the upper pole could not be safely dissected laparoscopically because it was too far from the esophagogastric junction or because of severe adhesions). Similar symptomatic outcomes were documented after 20 months.

If diverticulectomy is not necessary for symptomatic relief, endoscopic treatment for the motor disorder, such as forceful dilatation of the cardia, per oral endoscopic myotomy may be an attractive option. Initial results are promising, albeit mostly based on few case reports^[17,21-23].

Conservative treatment

Some ED are asymptomatic or present with few symptoms^[1]. This ED may be left untreated.

Some authors investigated the fate of untreated diverticula. Castrucci *et al.*^[18] followed up 13 patients for 64 months and showed no complications or worsening of pre-existing symptoms and no change in size (except for one case). Zaninotto *et al.*^[24] followed up 16 patients for 46 months in whom the conservative approach was followed because of the small size of the diverticula or the presence of severe comorbidities. Symptoms were mostly unchanged. The same authors reviewed the literature with similar results reported by five other studies^[25].

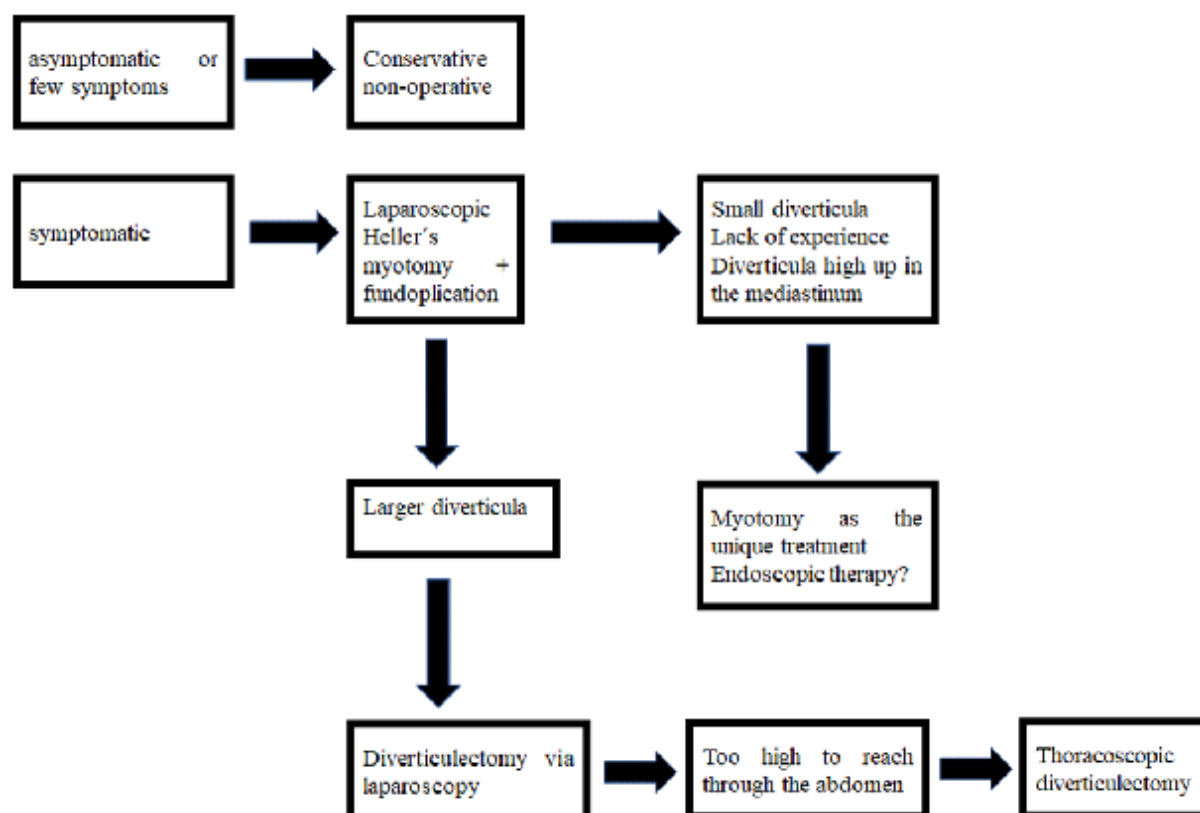


Figure 3. Schematic treatment selection tree diagram for epiphrenic diverticula

Some authors opt for treatment irrespective of symptoms due to the fear of aspiration of the contents of the diverticulum. Symptoms of nocturnal intermittent aspiration are frequent^[25]; however, cases of pneumonia are rare^[26,27].

The risk of malignant transformation is negligible and does not justify an operation in asymptomatic patients^[13].

CONCLUSION

ED treatment may be associated to high morbidity and mortality in up to 4% of cases^[18]. Thus, these patients should be preferably treated in centers with a high volume and expertise in esophageal surgery. A conservative nonoperative approach is acceptable in asymptomatic or oligosymptomatic patients since the risk for severe aspiration and cancer is exceptionally low. When surgery is indicated, the laparoscopic approach should be favored as results are similar to the thoracoscopy approach, but it allows the performance of a partial fundoplication to prevent pathologic reflux. Treatment of the underlying motor disorder is imperative to relieve symptoms and prevent leaks when a diverticulectomy is performed^[17], but the resection of the diverticulum may not to be necessary when they are small or very high up in the mediastinum. A treatment selection tree diagram is provided in Figure 3. Endoscopic therapy is waiting a careful evaluation but seems to be a promising alternative.

DECLARATIONS

Authors' contributions

Conception and design, acquisition of data, analysis and interpretation of data, drafting the article: Herbella FAM

Conception and design, review for intellectual content, final approval of the version to be published: Patti MG

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Meningiomas: criteria for modern surgical indications

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Abstract

The contemporary management of meningiomas is the result of the continuous evolution of neurosurgical techniques, along with the refinement of dedicated instrumentations. Above all, it is the magnification of the surgical view, thanks to the microscope and the endoscope, and their advancements, which allowed the improvement of surgical outcomes, in terms of both extent of resection and morbidity rates. Because of the benign nature of the vast majority of meningiomas, complete tumor resection is curative, and it is the gold-standard treatment. However, in the case of high risk of surgical morbidity, a less aggressive surgical treatment may be justified, also upon tailored analysis of the meningiomas' biological behavior and the improvements in postoperative strategies. The endoscopic technique plays a role, as a unique visualization tool or in combination with the microscope, in granting so-called maximum allowed resection. Considering the above, the most challenging task confronting modern meningioma surgery remains the selection of the most appropriate surgical approach, the latter greatly depending on location, anatomic tumor features, and relationships with critical neurovascular structures. Herein, we present a cogent analysis of the modern multifaceted indications for the endoscopic treatment of meningiomas, with a glimpse into the adjacent fields.

Keywords: Meningiomas, endoscopic-assistance, endoscopic endonasal, postoperative treatments



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INTRODUCTION

Meningiomas are the most common benign intracranial tumors, with an incidence rate reaching up to 98/100,000 individuals per year^[1-4]. They are much more prevalent than spinal meningiomas that account only for 1.2%-12.7% of all meningiomas and 25% of all spinal tumors. Meningiomas originate from arachnoidal (meningothelial) cells and, upon histological grading, the World Health Organization (WHO) recognizes benign grade I tumors (75%), atypical grade II meningiomas (20%-35%), and the malignant or anaplastic grade III subset (1%-3%)^[5]. The primary dural attachment site is another criterion for meningiomas classification. Intracranial meningiomas arise most commonly at the convexity (34.7%), often adjacent to the venous sinuses (22.3%), as compared to skull base tumors. Among infratentorial meningiomas, the majority (50%) are at the cerebellar convexity. Spinal meningiomas are most frequently located at the thoracic spine (67%-84%), followed by the cervical spine (14%-27%) and the lumbar spine (2%-14%). Initially proposed by Harvey Cushing and Louise Eisenhardt, the classification of meningiomas based on primary dural attachment helps describe the natural history, including the development of signs and symptoms, and the plan for an appropriate management strategy^[6]. Clinical presentation mostly depends on tumor size and location^[1,2,4]; tumors impinging the eloquent cortex often present with seizures, whereas skull base lesions more often present with cranial nerve deficits. Being a space-occupying lesion, all meningiomas can of course present with raised intracranial pressure. Spinal meningiomas may present with signs of acute or chronic spinal cord compression, neurologic dysfunction, and progressive myelopathy, according to the location. Seldom, meningiomas are found accidentally and without related symptoms, in ca. 3% of the population^[7]. Contrast enhanced MRI of the brain diagnoses and defines the details of meningioma; however, prediction of different histological subtypes of meningiomas is still not possible by conventional or advanced (diffusion-weighted imaging, perfusion imaging, and magnetic resonance spectroscopy) imaging techniques^[8,9]. Recently, radiomics-based machine-learning methods have rapidly become a promising technique for analyzing medical imaging in clinical oncology. By analyzing the spectral distribution of image pixels, valuable texture features of the meningioma, such as tumor cellularity, degenerative changes, and neovascularization, can be extracted and correlated to prognostic score^[10,11]. Continuous advances in radiomics will provide more information in regard to the tumor clinical behavior before surgery, with the potential impact of defining lesion clinical management.

Intracranial meningioma surgery with the goal of a radical resection has historically been performed through invasive surgical approaches with considerable associated morbidities; improvements in terms of both neurological outcome and extent of resection are the results of the continuous refinement of neurosurgical techniques^[12-15]. Nowadays, the surgical treatment philosophy for meningiomas is multifaceted, thanks to several adjuvant treatments, i.e., endoscopy, image-guided surgery, neuromonitoring, and radiosurgery. Moreover, recent developments of molecular biology have provided new information in terms of prognosis and indications to secondary treatments, thus leading to innovative, appropriate, and targeted adjuvant therapies granting better quality of life^[16-19].

Herein, we provide a cogent analysis of modern surgical indications for meningiomas, with special focus on the role of the endoscopic technique and with a glimpse into the continuous improvement of postoperative treatments.

SURGICAL INDICATIONS AND TECHNIQUES

Because of the benign nature of the vast majority of meningiomas, total removal leads to the most effective cure, and it is claimed as the gold-standard treatment. The impact of the extent of resection on tumor recurrence rates, traditionally categorized by the Simpson grading system, is the rationale behind aggressive surgical strategies for the management of meningiomas^[20]. However, the tumor often involves surrounding bone, dura, and neurovascular structures so that complete removal is challenging, sometimes risky, or even

impossible, especially in the attempt of minimizing morbidity related to the traits of the tumors^[2,4,7,17,18]. Nonetheless, tumor recurrence can occur, even with radical tumor removal and after long time from the primary surgery^[21-23]. For these reasons, treatment has moved toward more conservative surgical strategies for meningiomas, opting for a maximum allowed resection, minimizing risks for the neurological functional status, followed by strict imaging surveillance and eventual adjuvant therapies. This attitude shift, supported by a conspicuous amount of data demonstrating that tumor recurrence is a function of tumor biology, have questioned the clinical use of the Simpson grading score^[24-28]. This latter, indeed, has shown a prognostic value not suitable for all meningioma locations, achieving lesser prognostic impact for skull base and spinal meningiomas as compared to convexity tumors. Furthermore, the histological grade has recently been related to the location, and it has been observed that there is evidence of higher-grade meningiomas at hemispheric/convexity locations. This has to be taken into account when considering surgery for those tumors, which might feature favorable prognostic correlation between location and regrowth.

The ideal surgical approach should allow for maximum extent of resection, i.e., tumor mass removal in addition to infiltrated dura and bone, while minimizing the risk of morbidity. The choice of the most appropriate approach greatly depends on the anatomic features of the meningioma, its relationship with critical neurovascular structures, and the site of dural attachment.

Although the role of surgery for meningiomas might appear to be fairly standardized, class I scientific evidence is uncommon and surgical indications are mainly defined by experience-based practice^[16]: the surgical management of a meningioma, indeed, should be tailored upon its nature, symptomatology, patients' characteristics, and risk of morbidity. The observational management for asymptomatic, incidentally discovered meningiomas has been validated by many retrospective series and reviews^[7], while surgery is the main choice in cases of radiologically confirmed growth or in the presence of clinical symptoms. In the case of elderly patients and when lesions involve eloquent areas or deep and complex regions such as the cavernous sinus, radiotherapy can be considered as first-line treatment according to tumor size and signs^[16,29].

Finally, in the case of spinal meningiomas, the negligible benefits of an aggressive surgical strategy - that includes a wide removal of the dural attachment - do not seem to outweigh the risk of surgical complications and patients' morbidity, especially for ventrally located meningiomas or with calcified dural attachment^[23,28,30].

Meningioma surgery was revolutionized in the 1960s by the advent of the use of the operating microscope: the advancement of microsurgical techniques brought terrific improvement in terms of outcomes and definitely opened the era of modern neurosurgery^[31-33]. A new level of precision in the surgical removal of tumors, particularly skull base meningiomas, was reached and novel surgical routes have been experimented, with emphasis on a deep understanding of anatomy^[34,35]. Subsequently, further enthusiasm was brought by the advent of the endoscope in the late 1990s^[36-39]. The intrinsic optical properties of the endoscope, allowing for a wide and close-up view of the surgical field, added extra value to the safety of meningiomas surgical treatment, either as unique visualization tool or as an adjunct to the microscope.

The evolution of the surgical techniques and visualization tools moved along together with instrument development and technological advancements. From the bayonet-shaped instruments used for microsurgical approaches where the lens of the microscope is far from the surgical field, the endoscopic technique requires straight instruments that slide along the endoscope, whose lens is near the surgical target^[40,41]. Today's visualization tools are upgraded with sophisticated imaging technologies that enhance the capabilities to better identify the tumor-vessels interface, such as infrared technology,

with administration of intraoperative indocyanine green videoangiography. In meningiomas surgery, this intraoperative tool finds special application in parasagittal tumors^[42,43]. Maximal safe resection of parasagittal meningiomas is the goal of correct surgical treatment, and it is intimately related to the venous anatomy both near and directly involved by the tumor. Intraoperative indocyanine green videoangiography enables confirming sinus occlusion, removing the occluded portion of the sinus, and identifying and respecting the venous collateral circle.

Finally, in selected cases and alternative to the microscope, meningiomas removal can be performed under exoscope image guidance^[44].

Endoscope-assisted surgery

With increasing experience in skull base surgery, the concept of minimally invasive keyhole approaches flourished, intended not only as limited cranial opening but also as limited approach-associated surgical morbidity, achieved with less traumatism over the brain^[45]. The supraorbital route and a series of its modifications (the supraorbital eyebrow incision approach, the mini-supraorbital keyhole craniotomy, the transciliary approach, and the lateral supraorbital approach) epitomized the reconciliation of both concepts, benefiting from the tenets of minimal, efficacious access of keyhole approaches and those of maximal, effective, atraumatic brain exposures from skull base^[46-48].

The central difficulty of transcranial microsurgical keyhole approaches is the loss of intraoperative light and angle of view due to the limited craniotomy and the need of brain retraction. Continuous improvements in surgical visualization tools' technology led to modern endoscopy and neurosurgeons began using the endoscope as an allied adjunct to the microscope, for the purpose of bringing light and controlling manipulation in the depth of the operating field. Besides, the endoscope's assistance provides extended viewing angle and clear depiction of details in close-up view^[49].

The combined microscopic–endoscopic technique has demonstrated utility in two aspects of meningiomas skull base surgery: extension of the surgical field into additional intracranial compartments and visualization and resection of residual tumor not adequately visualized by the microscope around neurovascular corners. In particular, the endoscope allows the extension of posterior cranial approaches to the middle fossa through the tentorial incisura, increasing the resectability of Meckel's cave and petroclival meningiomas that often show a multi-compartment location, involving cavernous sinus, prepontine space, cerebellopontine angle, and lower clivus^[50-52]. During removal of such meningiomas, the endoscope enables tumor visualization at specific microscopic blind spots: the anterolateral surface of the brainstem, the entrance of the trigeminal nerve into the porous of Meckel's cave and of the VII-VIII cranial nerves into the internal acoustic meatus, and the jugular tubercle with the dural exit of the lower cranial nerves (IX-XI)^[53,54]. Thermal injury to neurovascular structures with the tip of the endoscope should also be taken into account^[51]. For the removal of anterior skull base meningiomas, the endoscope's assistance finds its main application when combined with the supraorbital approach^[51,55,56]. The endoscopic visualization discloses surgical corridors to reach the tumor that extends superior, lateral, and under the ipsilateral optic nerve and internal carotid artery, as well as the diaphragm sellae, without the need of splitting the Sylvian fissure. Endoscopic assistance increases the visualization of tumor parts within the olfactory groove that is otherwise limited by the orbital roof under the flat angle of view, as provided by the microscope.

Controversies remain about appropriate case selection, particularly with respect to the extended endoscopic endonasal approaches^[57-61]: the supraorbital route can be preferred for meningiomas with significant lateral extension, encroaching the supraclinoid internal carotid artery and its branches and/or extending laterally to the optic nerves that are outside the visibility and maneuverability of the endoscopic endonasal approach. Another criterion to choose the supraorbital approach is the preservation of olfaction that is

inevitably lost during endoscopic endonasal approaches to the cribriform plate. It is worth mentioning that patients harboring olfactory groove meningiomas frequently present with significant hyposmia and/or invasion of the lamina cribra and roof of nasal fossae: in these cases, the endonasal approach should be considered as a choice for surgical treatment. In patients with a subchiasmatic lesion and a prefixed chiasm, the endonasal approach is the preferred route because any transcranial approach would require retraction of the optic apparatus with the risk of visual decline.

Endoscope's assistance also finds application in convexity meningiomas located in critical areas. Rolandic and parasagittal meningiomas should be classified as higher risk tumors, as compared to other convexity meningiomas that are associated with low surgical complication rates^[2,4,62,63]. Even if maximal radicality has to be attempted because of a proven higher recurrence rate after partial resection, the more important goal is not to harm neurological functions. Radical resection may cause severe neurological impairment because of direct mechanical trauma to the eloquent areas, especially if the tumor is tightly adhering to the cortex and/or because of vascular arterial and venous impairment. The close-up view provided by the endoscope may be helpful in the identification of the arachnoid plane at the tumor-cortex and tumor-vessels interfaces and can contribute, together with the more established role of electrophysiological mapping and intraoperative videoangiography, to pushing the boundaries of the maximal safe resection in both achieving the best functional results and reducing the tumor remnant volume^[42,63].

Lastly, endoscopic spine surgery as an alternative to various open neurosurgical techniques gained popularity in the management of degenerative disc diseases, while its application in treating spinal meningiomas and other intradural lesions remains rather sparse^[64,65]. The surgical procedure includes access to the spine using tubular ports, parallel or expandable depending on the size of the lesion, thus obviating the need of long skin incisions, paraspinal muscle dissection, and destabilizing dissection of ligamentous structures. Tumor resection is achieved through small bony fenestration under endoscope-assisted microscopic visualization, with occasionally reported pure endoscopic surgical procedures. The benefits of the endoscope become particularly evident in the removal of intradural tumors located anterolaterally to the spinal cord. The endoscope can obviate the use of much more complex anterior routes to the spine, often associated with postoperative spinal deformity and the need for adjunctive fusion surgery, allowing for visualization and removal of the ventrally located part of the tumor, with minimal retraction of the spinal cord. Endoscopic surgery may result equally effective in terms of extent of resection and with similar morbidity compared to open techniques^[30,66]. The safety of spinal meningiomas removal is increased by the use of intraoperative neuromonitoring that enables the continuous evaluation of the sensory and motor functions of the spinal cord by means of somatosensory-evoked potentials, motor evoked potentials, and D-waves^[66]. Therefore, intraoperative neuromonitoring should be considered as part of spinal meningiomas surgery, regardless of the surgical approach.

Endoscopic endonasal surgery

Since the 1990s, continued improvements in illumination and magnification have led to the purely endoscopic transsphenoidal approach to the sella, a development that has subsequently revolutionized the treatment of lesions accessible through the skull base^[42,43,67]. The introduction of extended endoscopic approaches, technological advancements as well as improvements in skull base reconstruction techniques, and increased experience have established the endoscopic endonasal approach as an important option for anterior skull base meningiomas^[68-73]. With further expansion of indications, in very selected cases, this approach has entered into the broad spectrum of surgical options for cavernous sinus, petrous ridge, and anterior foramen magnum meningiomas^[74-76].

The endonasal approach for anterior skull base meningiomas has several advantages and special anatomic considerations to be underlined^[69,71,77-81]. Aside from the cosmetic benefit of avoiding external scars, the

endonasal corridor is a direct path to the tumor, avoiding the need for brain retraction and reducing the manipulation of neurovascular structures on the way to skull base. As part of the approach, an extensive bony and dural resection is achieved and the major vascular supply to the meningioma is addressed before the tumor excision. The main advantage of this surgical route is related to the possibility of achieving an early decompression of the optic apparatus that seems to be associated with more favorable visual outcomes. This is particularly true for tuberculum sellae meningiomas that usually present with visual disturbance because of the intimate anatomical relation between the tumor and the optic apparatus. The endoscopic endonasal technique allows for reduced manipulation of the compressed optic chiasm, and an improved visualization and preservation of perforating vessels. In addition, it provides direct exposure of the inferomedial aspect of the optic canals, allowing for quick decompression in cases of tumor extending within. The main drawback remains the skull base reconstruction, whose failure results in cerebrospinal fluid leakage and its related complications. In recent years, skull base repairing techniques including fat grafts, synthetic materials, and vascular flaps (e.g., the pedicled nasal-septal flap) continue to improve, expanding the indications for these approaches^[82-84].

Patient selection is critical for the success of an endoscopic endonasal approach. The question of which tuberculum sellae meningioma should be resected transcranially and which should be approached transsphenoidally remains paramount. Several series have compared approaches and attempted to define which patients are best suited for each approach^[61,68,85-89]. Larger tumors (> 3 cm) usually extend into multiple areas, making complete removal through the transsphenoidal route challenging. Similarly, tumors with encasement of the carotid arteries and/or anterior communicating artery complex, in the absence of arachnoid plane between the tumor and the surrounding encased vessels, predicts more difficult resection and may limit the efficacy of the endoscopic endonasal approach. The degree of tumor invasion into the optic canal can be a relevant item when choosing the surgical route: whether invasion of the medial inferior and superomedial aspects is present, transsphenoidal approach can be an option, but, if extensive circumferential invasion is present, a craniotomy approach might be necessary. The role of the endoscopic endonasal approach in the treatment of olfactory groove meningiomas is much more controversial and it is still a matter of discussion in the current literature^[69,85,90-92]. In patients with adequate preoperative olfaction, the endonasal should be not preferred; conversely, the endoscopic approach offers supplementary value for staged or combined procedures in the surgical management of giant olfactory groove meningiomas with significant extension into the nasal cavities and paranasal sinuses.

Finally, advancements in endoscopy have further extended the possibilities of moving to regions outside the nasal sinuses, namely the orbit and the speno-orbital area. The endoscopic superior eyelid transorbital corridor has recently been explored as a feasible route to address selected lesions at lateral middle fossa and superolateral orbital region, with limited intracranial extension^[93-96]. In meningiomas surgery, this approach finds its main application in *en plaque* speno-orbital tumors. Resection of *en plaque* meningiomas of the skull base through transcranial approaches can cause significant morbidity, and complete removal is often unattainable. The endoscopic transorbital approach has proven to be effective in greater sphenoidal wing's hyperostosis debulking, which is usually responsible for patient's proptosis, oculomotor, and visual impairment, due to optic canal, superior orbital fissure, and orbital compression. In these cases, clinical benefit is the goal of surgery, rather than complete tumor removal. Extent of resection and symptoms relief can be implemented by the combination with the endonasal transsphenoidal approach, which allows for drilling of the medial optic canal and lamina papyracea removal. Further studies with longer follow-up are needed for a better definition of the pros and cons of this approach compared to more traditional transcranial ones.

ADVANCES IN POSTOPERATIVE TREATMENTS

In the contemporary era, surgery remains the cornerstone of treatment for meningiomas. At the same time, advances in imaging, treatment planning, and radiation delivery techniques have dramatically

changed irradiation of these tumors and fractionated radiotherapy and radiosurgery have entered the armamentarium of modern neurosurgery. Advances in the molecular characterization of meningioma have enabled the identification of genetic alterations and methylation profiling subclasses that correlate with the likelihood of tumor recurrence and represent promising medical therapy targets^[97,98]. Thus, genomics has altered the understanding of the molecular underpinnings of meningiomas, and ongoing clinical trials have the potential to alter how meningiomas are treated.

The high local control rates with low morbidity achieved by radiation modalities and the surgical philosophy of maximal safe resection for meningiomas associated at higher risk of morbidity should guide the best treatment options in a patient-based and lesion-specific approach. Radiotherapy is currently adopted as first-line treatment for cavernous sinus meningiomas, due to increased complication and mortality rates associated to surgical resection^[16,29]. For adjuvant radiotherapy, the goal of treatment is preventing progression to higher-grade malignancy and decreasing recurrence rate. In cases of grade II (atypical) and grade III (anaplastic/malignant) meningiomas, there is a substantially greater risk of recurrence and a clearer role for adjuvant radiotherapy, even following a gross total resection. It is important to note that recommendations for radiotherapy in different meningioma scenarios, coming from the European Association of Neuro-Oncology (EANO) and the Current National Comprehensive Cancer Network (NCCN), do not take into account tumor location or any molecular pathological markers, and both were published prior to the revised 2016 WHO classification, whose criteria may result in more WHO grade II meningiomas that would have been classified as grade I under the older criteria^[16,99].

CONCLUSION

The continuous evolution of the surgical techniques and, above all, the magnification of the surgical view provided by the endoscope have brought terrific contributions to the effectiveness of meningioma surgery. The most challenging task confronting modern meningioma surgery remains the selection of the most appropriate surgical approach: multiple factors including tumor size consistency and location, extent of dural attachment, and relation with neurovascular structures, along with surgeon's preference and experience, should be taken in account. With the amount of support and guidance that current technologies and advances have provided, modern criteria for meningioma treatment should further consider the careful balance between the desired goal of meningioma surgical cure, and the patient's neurological function preservation should guide the surgery. Improvements in radiation therapy modalities and advances in the molecular characterization of these tumors will further refine the criteria for the surgical approach to meningiomas.

DECLARATIONS

Authors' contributions

Made substantial contribution to conception of the study: Cappabianca P, Solari D

Prepared the manuscript draft: d'Avella E

Critically revised the final version of the manuscript: Cappabianca P, Cavallo LM

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Review

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Robotic or laparoscopic surgery for rectal cancer - which is the best answer? A comprehensive review of oncological outcomes

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Abstract

Treatment of rectal cancer is ever evolving with the introduction of newer surgical technologies and multimodal treatment approach. The literature evaluating the various surgical treatment options with regards to operative and nonoperative outcomes is abundant. This is a comprehensive review focused on oncological outcomes of rectal cancer resection performed robotically or laparoscopically. Based on the current literature available, there is no significant difference in total mesorectal excision completeness, lymph node harvest, positive circumferential resection margin, or proximal resection margin between robotic and laparoscopic approaches for rectal resection. Selection of surgical approach should not be based on pathological outcomes as they are equivalent.

Keywords: Robotic, robotics, laparoscopic, laparoscopy, rectal cancer, rectal carcinoma, total mesorectal excision

INTRODUCTION

The treatment of rectal cancer has evolved during the last several decades into a multidisciplinary model of care. During this time, surgical innovations continued to revolutionize treatment and improve patient outcomes, most notably the introduction of total mesorectal excision (TME) by Heald *et al.*^[1]. This landmark discovery changed the trajectory of rectal cancer resections and greatly improved patient outcomes by reducing pelvic recurrences. Since that time, laparoscopic TME was introduced and has



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now become standard of care after several large randomized controlled trials (RCTs) assessed oncologic outcomes and early postoperative recovery^[2-8].

Performing a laparoscopic TME is not without its challenges, especially in a deep narrow pelvis with the two-dimensional view and limited dexterity. Robotic TME was introduced to overcome some of these challenges. The theoretical technical advantages of robotic TME include a stable camera platform, three-dimensional view, and better articulation of the surgical instruments^[9]. Although this technology has gained widespread popularity, it is not without its own set of challenges, including higher cost, longer operative time, and loss of tactile sensation.

Surgical innovation continues to play a vital role in the multimodal treatment of rectal cancer. Examining the pathologic outcomes is important to ensure appropriate care is provided when introducing new technologies. To date, the largest RCT available to compare laparoscopic and robotic rectal resections is the ROLARR trial^[10]. Several other RCTs are now available, along with numerous meta-analyses to further evaluate the literature on pathologic outcomes with robotic compared to laparoscopic rectal cancer resections, which are discussed in this review. This review is Part 2 of a two-part series, in which the non-oncologic outcomes and learning curve are separately discussed.

Pathologic outcomes

Total mesorectal excision grade

When assessing pathologic outcomes for rectal cancer, the completeness of the TME is one of the important oncologic factors to consider. It is also a useful marker to compare the effectiveness and safety of the various surgical techniques, such as laparoscopic and robotic. The three RCTs discussed below on robotic *vs.* laparoscopic approach for the treatment of rectal cancer have assessed TME grade or completeness and none have shown a significant difference in the quality of TME specimen^[10-12]. Furthermore, multiple meta-analyses have also shown no significant differences.

The ROLAAR RCT trial included TME pathology specimen grading using the method of Quirke and Dixon for completeness and found complete TME in 77.6% of laparoscopic specimens *vs.* 76.4% of robotic specimens ($P = 0.14$)^[10]. A phase II open label prospective RCT also assessed the quality of TME by a pathologist, as the primary outcome and found similar results: complete TME 78.1% (laparoscopic) *vs.* 80.3% (robotic) and near complete in 21.9% (laparoscopic) *vs.* 18.2% (robotic) ($P = 0.599$)^[11]. They did, however, note one incomplete TME (1.5%) in the robotic group and none in the laparoscopic group. Lastly, a smaller pilot RCT also found no difference in macroscopic judgement of the TME specimen with complete TME noted in 17 of 18 robotic samples and 1 nearly complete *vs.* 13 of 16 complete TME and 3 nearly complete ($P = 0.323$)^[12].

A recent meta-analysis by Eltair *et al.*^[13] assessed the robotic and laparoscopic approaches for the treatment of rectal cancer within nine RCTs that included 1463 patients (728 robotic *vs.* 735 laparoscopic)^[13]. Four RCTs were included in the macroscopic assessment of complete TME, including the three discussed above. They found no statistically significant difference in complete resection with zero heterogeneity in their assessment. Simillis *et al.*^[14] compared open *vs.* laparoscopic *vs.* robotic *vs.* transanal mesorectal excision for rectal cancer in their meta-analysis and included 29 RCTs. The authors reported significantly higher incomplete or nearly complete TME in the laparoscopic *vs.* open group (odds ratio of 1.52), but no differences in the laparoscopic *vs.* robotic (odds ratio of 0.98) approaches. A recent network meta-analysis assessed the quality of TME and reported no difference in complete mesorectum excision in the pooled analysis of 11 studies^[15]. Nine studies were included in the pooled analysis examining near-complete mesorectal excision and also reported no difference when comparing laparoscopic *vs.* robotic methods.

One meta-analysis that included 12 studies (11 case-control and only 1 RCT) did find a higher complete TME in robotic vs. laparoscopic surgery (odds ratio of 1.83, $P = 0.03$), however there was significant heterogeneity noted in the analysis ($I^2 = 47\%$)^[16]. Furthermore, this analysis included a majority of case-control studies, which are of lower level of evidence, while other meta-analyses have included more RCTs and prospective studies.

Lymph node harvest

The current guidelines, including those of the American Joint Committee on Cancer (AJCC) and College of American Pathologists (CAP), recommend a minimum of 12 lymph nodes be examined to accurately stage rectal cancer in order to aid in the decision for adjuvant treatment^[17-19]. The reasons for low lymph node harvest can include neoadjuvant treatment, lack of high ligation of the vessels, and potentially poor surgical or pathologic technique. When comparing surgical approaches for rectal cancer, it is important to evaluate lymph node harvest with each technique.

The ROLARR RCT performed an intention to treat analysis in which one of the outcomes measured was median lymph nodes retrieved^[10]. They reported no differences; both groups yielded a high number of lymph nodes: 24.1 (laparoscopic) vs. 23.2 (robotic), almost double the minimal requirement. Kim *et al.*^[11] noted a higher number of lymph nodes in the robotic (median 18) compared to the laparoscopic group (median 15) ($P = 0.04$) in their RCT. They also examined the rate of 12 or more lymph nodes retrieved in their groups and found 90.9% of patients achieved this benchmark in the robotic group compared to 74% of patients in the laparoscopic group. Of note, the majority of patients in this single-center RCT received preoperative chemoradiation (77.3% in robotic vs. 77.5% in laparoscopic), which might have led to the lower number of lymph nodes.

A seven-institution multicenter study examined consecutive patients who underwent robotic or laparoscopic intersphincteric resection for low rectal cancer^[20]. Propensity score analysis was performed with 1:1 case-match, in which no difference was found in the number of lymph nodes retrieved ($P = 0.126$) or the number of positive lymph nodes ($P = 0.712$). Kim *et al.*^[21] also used propensity score matching to analyze their retrospective cohort and, after matching, found no difference in the number of harvested lymph nodes ($P = 0.44$). Furthermore, a propensity score match study was performed in consecutive obese patients who underwent laparoscopic or robotic rectal resection at three centers, and no difference was noted in the mean lymph node yield (17 in robotic vs. 16 in laparoscopic, $P = 0.639$)^[22]. A single-center study examined their prospectively collected database of mid to - distal rectal cancers and found a higher median number of lymph nodes harvested (12 in laparoscopic vs. 14 in robotic, $P = 0.002$)^[23]. However, the groups however were not matched between the median tumor distance of 8 cm in laparoscopic vs. 7 cm in robotic. Moreover, there were more male patients, more comorbidities, and preoperative radiation in the robotic surgery group.

Multiple meta-analyses examining the highest level of evidence available in the form of RCTs have found no difference in the number of lymph nodes retrieved when comparing laparoscopic and robotic surgery for rectal cancer^[13-15,24,25].

Margins

Rectal cancer specimen margins assessed are circumferential radial (CRM), proximal, and distal. Ensuring negative margins is of utmost importance in reducing local recurrence rates. Margin assessment is used as a marker to examine and compare surgical techniques. The literature on robotic vs. laparoscopic rectal resection for each margin status is discussed below.

Circumferential Radial Margin: The largest RCT to date on robotic vs. laparoscopic resection for rectal cancer is the ROLARR trial^[10]. In total, 237 patients were randomized to robotic, of whom the CRM

status was available for 235, and 234 to laparoscopic with CRM status available for 224 patients. The CRM positivity rate was 6.3% in laparoscopic vs. 5.1% in the robotic group ($P = 0.56$). Kim *et al.*^[11] also found similar CRM positivity rates in their RCT with no difference in robotic (6.1%) compared to laparoscopic (5.5%) ($P = 0.999$). Eltair *et al.*^[13] also confirmed no difference in positive CRM in their pooled analysis of three RCTs in their meta-analysis, but high heterogeneity was noted ($I^2 = 57\%$). Several meta-analyses that included retrospective studies along with the available RCTs have also shown no difference in positive CRM^[14,24-26].

Proximal Resection Margin: Adequate mobilization of the colon, including splenic flexure mobilization, should allow for sufficient proximal resection margins in rectal cancer surgery. The advantages of laparoscopic and robotic rectal cancer resection with this regard pertain to the smaller incisions required for sufficient mobilization compared to open surgery. The three RCTs examined in this review by Jayne *et al.*^[10], Kim *et al.*^[11], and Baik *et al.*^[12] reported no difference in proximal resection margins when comparing robotic to laparoscopic rectal cancer operations. None of the meta-analyses examined in this review reported a difference in proximal margins^[13,14,27,28].

Distal Resection Margin: The ROLARR RCT did not compare length of distal margin between the two surgical groups but did note one patient had a positive distal margin in the laparoscopic group^[10]. Kim *et al.*^[11] reported median distal resection margins and noted no statistical difference between robotic (1.5 cm) and laparoscopic (0.7 cm) ($P = 0.11$). Baik *et al.*^[12] also noted no difference in mean or median distal resection margins in their groups ($P = 0.467$). Eltair *et al.*^[13] examined five RCTs, which included 455 patients, in their meta-analysis for distal resection margins and found slightly longer distal margins in the robotic group compared to the laparoscopic one with a mean difference of 0.8 cm ($P = 0.004$). There was significantly high heterogeneity ($I^2 = 75\%$) observed in this pooled analysis. A meta-analysis by Liao *et al.*^[27] included five RCTs, with 340 patients, and also found longer distal margin in the robotic group compared to the laparoscopic one ($P = 0.003$), but again high heterogeneity was noted ($I^2 = 75\%$). Simillis *et al.*^[14] also found the robotic surgical approach to have higher distal resection margins when compared to open (7.6 mm), laparoscopic (6.8 mm), and transanal (6.8 mm) techniques. There were no reported data on positive distal margins for any of these groups.

CONCLUSION

Introduction of new surgical techniques to further surgical innovation and improve patient outcomes should be judiciously undertaken to ensure patient care, most notably that oncologic outcomes are not compromised. The majority of the high-level available evidence has found no differences between the two surgical approaches relative to TME completeness, lymph node harvest, positive CRM, or proximal resection margin. A longer distal resection margin has been found with robotic compared to laparoscopic approaches in meta-analyses, but not in RCTs. However, there is no evidence that a longer distal margin translates to better oncological outcomes.

Based on the current literature, either approach, laparoscopic or robotic, is safe and effective from a pathology standpoint. Since the two techniques are comparable, other outcomes and factors need to be considered when recommending one versus the other to our patients. The non-pathology outcomes are discussed in a separate review and should be strongly considered^[29].

Scrutinizing ones' own rectal cancer resection outcomes is even more important than reviewing the literature. The Commission on Cancer's National Accreditation Program for Rectal Cancer was established to ensure the highest quality metrics based on the highest level of evidence available are followed^[30]. The NAPRC requires data collection and monitoring, which should help the provision of optimal care. A national program of this caliber allows for further tracking of current care processes to better evaluate

the care model to continue improving patient care. Regardless of what surgical technique is chosen by the surgeon, a multidisciplinary team approach must be applied to optimize oncologic outcomes^[31,32].

DECLARATIONS

Authors' contributions

Manuscript preparation: Ghuman A, Kavalukas S

Manuscript review and editing: Wexner SD

Availability of data and materials

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Dr. Wexner is a paid consultant and receives royalties for intellectual property license from Intuitive Surgical, Medtronic, and Karl Storz and is a paid consultant for Stryker, Takeda, and Baxter. All other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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Editorial

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Awake minimally invasive surgery as a game changer in lung cancer

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Abstract

Surgery still offers the best option for patients with early stage non-small cell lung cancer that can tolerate surgery. With the increase in screening programs, more patients are diagnosed at early stages of cancer. Sadly, not all of them are fit for surgery, but with minimally invasive approaches, large number of those patients can be offered surgery and get a better overall survival. Awake non-intubated video assisted thoracic surgery resection is one of the most recent technique that we believe to be a game changer in this spectrum of patients who were previously classified as medically inoperable.

Keywords: Video assisted thoracic surgery, stereotactic body radiotherapy, early stage, non-small cell lung cancer, minimally invasive, inoperable

INTRODUCTION

With an increase in the number of patients diagnosed with early stage lung cancer, options for cure include surgery and stereotactic body radiotherapy (SBRT). Recent guidelines published from ASTRO recommend the use of SBRT in cases that medically inoperable^[1]. These results were augmented by the most recent publication that found that median survival was significantly greater after surgery compared to SBRT in a risk-adjusted matched cohort of patients judged to be surgical candidates. The authors recommend



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that every operable patient considering primary SBRT should be educated regarding this difference in survival^[2]. Even though this was a retrospective study, it makes a real clinical trial to compare both maneuvers very difficult. Such a trial that will contain two very different patient populations, one group will be fit for surgery and the other one is unfit, with a significant bias regarding long-term outcomes and overall survival. Surgery still offers the best option for patients that can tolerate it^[3]. With the increase in minimally invasive approaches, more patients can be offered surgery and achieve better overall survival. Awake non-intubated video assisted thoracic surgery (VATS) resection is one of the most recent technique that we believe to be a game changer in this spectrum of patients who were previously classified as medically inoperable.

CHALLENGES WITH EARLY STAGE LUNG CANCER

As more screening programs become readily available for lung cancer, more patients are diagnosed with early stage lung cancer^[4]. Most of these patients have very mild or no symptoms, making it troublesome for physicians to ask them to consider high risk or very complex interventions. However, at the same time, these patients mostly have comorbidities that increase with age such as cardiovascular problems and limited pulmonary reserves, and even if we can offer them curative surgery, a large percentage of them are medically inoperable. There was no specific definition of such inoperability. With an average age of diagnosis of 70 years^[5], lung cancer patients often have a level of baseline frailty, along with concomitant comorbid conditions, especially those associated with risk factors for non-small cell lung cancer such as heart disease, chronic obstructive pulmonary disease, and loss of pulmonary parenchyma. Age is not the sole factor to determine medical operability, several factors such as performance status, presence of medical comorbidities, and pulmonary function tests, contribute to overall risk assessment.

With this above-mentioned status, surgeons try to improve the overall perioperative experience and facilitate surgery for more lung cancer patients by moving from open surgery to less invasive surgery. In thoracic surgery, there was a rapid pace of change from open thoracotomy to multiport VATS, uniportal VATS, and subxiphoid VATS, all aiming at decreasing the surgical burden on the patients by decreasing the incision and limited access surgery. Yet, there was another important factor that attributed to mortality and morbidity and that was anesthesia. Since the development of minimally invasive lung resection, almost all cases were operated under general anesthesia with double lumen endotracheal intubation. Tracheobronchial injuries^[6-8], prolonged effect of neuromuscular blockers^[9], and pulmonary complications postoperatively^[10] are all possible complications of general anesthesia and double lumen endotracheal intubation. This drove surgeons to think of non-intubated VATS as a way to avoid these complications and improve the patients' overall experience. This seems to have an extra advantage in patients with impaired pulmonary function who are usually unfit for general anesthesia and will typically be deferred to another therapeutic option inferior to radical curative surgery.

Another challenge appears on the surface is the ground glass opacities (GGOs) which become more detected nowadays thanks to screening programs. Incidence of cancer in GGO has been reported as high as 63% so most surgeons prefer to get a biopsy before resection, but some prefer direct surgical resection. This can be possible for peripheral lesions, but for central GGOs it is very challenging to obtain a preoperative pathology. Hence, a minimally invasive approach can offer both diagnostic and therapeutic solutions that cannot be done with the SBRT approach^[11]. Even in peripheral GGOs, localization in non-collapsed lung or emphysematous patients is limited especially with coughing and movements of the diaphragm and the mediastinum in case of awake VATS. This can be overcome by intrathoracic vagal and phrenic nerve blocks or administration of aerosolized lidocaine. For nodules and GGOs not amenable to finger palpation, preoperative CT guided hook wire insertion or a preoperative CT-guided dye localization can improve the intraoperative localization and shortened the operative time and manipulation^[12].

AWAKE VATS: WHAT CAN BE OFFERED

Surprisingly, awake thoracic surgery is not a brand-new intervention. The idea dated back to 1923 to Eloesser^[13] who, in his report in California State Journal of Medicine, stated that, "...almost all operations upon the bony thorax should be done under local and regional anesthesia..." With the improvements in general anesthesia and tracheal intubation, regional and local anesthesia vanished gradually^[14] till the evolution of VATS in the early 1990s when more surgeons showed increased interest in keeping the patients breathing spontaneously with some degree of awareness to avoid the problems associated with general anesthesia and double lumen endotracheal intubation^[15]. Later, surgeons started to look for the postoperative lymphocyte responses and other immune responses in cases of awake versus conventional general anesthesia, and they demonstrated attenuated stress response after awake VATS in comparison to an equivalent procedure performed under general anesthesia and one-lung ventilation^[16,17]. This in turn attracted more surgeons to adopt this technique in cancer surgery as lower immune system responses are highly desirable in those patients. In 2014, Gonzalez-Rivas^[18] published the first report of awake uniportal VATS lobectomy. Two years later, the Tor Vergata group published the first series of 1000 patients operated using awake uniportal VATS^[19]. Moreover, the development of uniportal VATS in conjunction with awake surgery helped to perform some operations in the outpatient setting^[20]. Non-intubated VATS can be non-intubated with deep sedation in which patients are relaxed with good airway control via facemask, nasal cannula, or even laryngeal masks. This type awake VATS is suitable for major resections with longer operative time. The second type is loco-regional anesthesia in awake patients and this is commonly used for diagnostic VATS and minor resections^[21,22].

FUTURE PROSPECTIVE

This contentious effort drove more surgeons to use this technique in more frail and high risk surgery patients. Wang *et al.*^[3], in Taiwan, retrospectively investigated the results of 28 patients with impaired lung function (preoperative forced expiratory volume in 1 second < 70% of the predicted value) who underwent non-intubated VATS. Only eighteen patients in this series had primary lung cancers, of those patients, lobectomy was performed in 4, segmentectomy in 3, and wedge resection in 11, with lymph node sampling adequate for staging. Wang *et al.*^[3] reported no mortalities after 30 days; however, conversion to tracheal intubation and one-lung ventilation was required in one patient, an 80-year-old man, because of persistent intraoperative wheezing and labored breathing. The intubation was performed smoothly in the lateral position. He required ventilator support postoperatively but was weaned off the next morning. No patients required conversion to a thoracotomy or blood component therapy. This report gives hope that some patients, previously categorized with impaired pulmonary function and medically inoperable patients, can now safely be offered a curative surgery. Yet, sharp cardiac and pulmonary indications for awake non-intubated surgery have not been fully investigated and are still under trials to determine the exact cut-off values. The most accepted contraindications so far for awake or non-intubated uniportal VATS can be categorized into: (1) patient related (i.e., obesity, neurological conditions, uncontrolled gastroesophageal regurgitation, central hypoventilation syndrome, persistent cough or mucus retention, and hemodynamically instable or severely hypoxia/hypercapnia); (2) anesthesiologist-related (i.e., difficult intubation, technical contraindications to general anesthesia, need to protect the contralateral lung from spillage of endobronchial contents, and inexperienced or non-cooperative team); and (3) surgeon-related (i.e., uniportal VATS experience and previous operations with adhesions)^[23].

Khorfan *et al.*^[2] retrospectively investigate records from 2004 to 2016 of patients who were fit for surgery, but refused to have surgery and preferred SBRT. From 138,143 patients who met our inclusion criteria, they found that 1359 patients (0.98%) refused recommended surgery and elected SBRT. Numbers are increasing every year. Propensity matching resulted in 1,315 well-balanced pairs. Surgery was associated with higher median survival (74 months *vs.* 47 months; $P < 0.01$) in the matched cohort. Survival benefit persisted

after adjusting for covariates on Cox regression (hazard ratio, 1.69; $P < 0.01$). The authors concluded that, operable patients considering primary SBRT should be educated regarding this difference in survival. Even though they reported that in the surgery group, 102,596 (75.0%) underwent lobectomy and 25,048 (18.3%) sub-lobar resection with the remaining patients undergoing other or unspecified types of resection, they did not report how many patients who refuse surgery were offered minimally invasive surgery, or whether they were offered lobectomy or sub-lobar resection and whether this was a point of refusal for surgical option or not. According to Sihoe^[24], for any new technique or procedure, the evolution of research and evidence-gathering can be categorized into five distinct phases that neatly correspond to the development of a human. Awake uniportal VATS must go to from Infancy-safety & feasibility and Childhood-crude benefit to the next level of technique maturity in this stage which is Adolescence-objective, quantifiable benefit then to Adulthood-treatment efficacy and finally to Maturity-sustainability.

CONCLUSION

Although there is cumulative evidence of the safety and feasibility of awake uniportal VATS lung resection for early stage lung cancer and the preliminary results suggesting benefits for patients with limited pulmonary functions, more prospective studies are needed to investigate long-term outcome on patients who have limited pulmonary reserve and increased frailty.

DECLARATIONS

Authors' contributions

Collection and assembly of data, data analysis and interpretation: Elkhayat H

Manuscript writing: Elkhayat H, Gonzalez Rivas D

Conception and design, administrative support, provision of study material: Gonzalez Rivas D

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Review

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Sublobar minimally invasive surgery vs. stereotactic ablative radiotherapy for early stage non-small cell lung cancer

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Abstract

Although lobectomy has been traditionally considered the standard treatment for early stage non-small cell lung cancer (NSCLC), lung-sparing resections usually called “sublobar resections” have exponentially increased in their use in the age of minimally-invasive surgery. Sublobar resection, especially anatomical segmentectomy, has shown comparable oncological outcomes in tumors less than 2 cm in diameter without nodal involvement and distant metastasis. On the other hand, more advanced radiation techniques such as stereotactic ablative radiotherapy, have shown excellent local control rates in stage I NSCLC, with low rates of post-treatment complications, so not only is its role growing in inoperable patients, but also in standard-risk stage I patients. There is a need for multicenter randomized trials addressing specifically this issue. This review aims to collect comparative data about the outcomes of both treatment strategies in early stage NSCLC.

Keywords: Thoracic surgery, video-assisted, stereotactic radiation therapy, lung neoplasms

INTRODUCTION

Lung cancer is still the leading cause of death by cancer with 1.8 million deaths in 2018^[1]. Stage I non-small cell lung cancer (NSCLC) shows a 5-year overall survival (OS) ranging from 68% to 92% in clinical



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stage I^[2]. Since the Lung Cancer Study Group (LCSG) in 1995, lobectomy became the standard pulmonary resection for standard-risk surgical cases^[3]. Since then, several comparative studies have shown that anatomical sublobar resections (SLR) in selected cases (early stage carcinoma less than 2 cm, in peripheral location without nodal involvement, especially when ground-glass appearance or long duplication time have been observed) shows similar outcomes to lobectomy in terms of disease-free survival (DFS) and OS^[4-8], so the role of SLR is growing exponentially from the high-risk and inoperable patients to also elective cases without pulmonary or cardiovascular compromise (i.e., intentional SLR). Stereotactic ablative radiation therapy (SABR), also known as stereotactic body radiation therapy (SBRT), has also shown a role for inoperable stage I NSCLC with acceptable survival outcomes^[9-11] and better postoperative morbidity profiles. However, there is still a lack of prospective randomized trials comparing specifically SLR with SABR, so level 1 evidence is still missing^[12]. The aim of this review is to collect and discuss all the evidence available regarding this controversial issue.

STEREOTACTIC ABLATIVE RADIATION THERAPY

SABR differentiates from conventional radiotherapy treatments in delivering larger doses of radiation per session. A typical SABR course for stage I NSCLC consists of 1 to 5 treatments over a 1 to 2 week time period with daily doses of 10 to 34 Gy, while a conventional daily dose of radiation therapy is 2 Gy, which is typically given 5 days a week for approximately 6 weeks.

There are some studies comparing standard radiotherapy and SABR. The SPACE trial randomized 102 patients to receive SABR 66 Gy (3 fractions, 1 week) or three dimensional conformal radiation therapy (3DCRT) 70 Gy (7 weeks). There were no significant differences in terms of OS and progression free survival (PFS) between both arms, with a tendency of improved disease control rate in the SABR arm, as well as less toxicity and better quality of life^[13]. Li *et al.*^[14] conducted a meta-analysis comparing conventional radiotherapy to SABR in inoperable stage I NSCLC. They found better OS (HR = 0.66; $P < 0.00001$), PFS (HR = 0.34; $P < 0.00001$), and lung-cancer specific survival (HR = 0.42; $P < 0.00001$). SABR showed lower rate of adverse events in terms of pneumonitis, esophagitis, and dyspnea. A systematic review published in 2017 also found SABR to be better in terms of survival and local control compared to other techniques of radiotherapy, as well as less toxic^[15].

One advantage is the shorter treatment duration. The increased doses of radiation also make SABR more potent and achieve higher rates of local tumor control in stage I NSCLC^[12]. Indeed, prospective studies and propensity score comparisons have consistently shown 3-year local control rates of approximately 90% with SABR for stage I NSCLC^[11,16,17]. Toxicity is low after SABR, with symptomatic radiation pneumonitis (grade ≥ 2) - usually consisting of mild fatigue - ranging between 7%-16%^[18,19], chest wall toxicity (pain and rib fractures), decreased pulmonary function, and less commonly, esophagitis, skin irritation, and brachial plexopathy in apical tumors.

One more potential advantage of SABR compared to surgical treatment is that overall quality of life is usually not affected after the treatment. The use of less intense fraction schemes is recommended for more central tumors to avoid more severe adverse effects such as hemoptysis, pneumonia, and respiratory failure.

As SABR induces lung damage and does not resect the tumor, surveillance requires careful imaging tests to assess ground-glass opacities, consolidation, and nodular growth in relation to primary site, but local control rates at 3 years are about 90%^[11,17]. Intralobar failures after therapy are 15%^[12] and regional recurrence 9.6%^[20], with distant recurrence as the most common pattern of recurrence, raising up to 25% of treated cases.

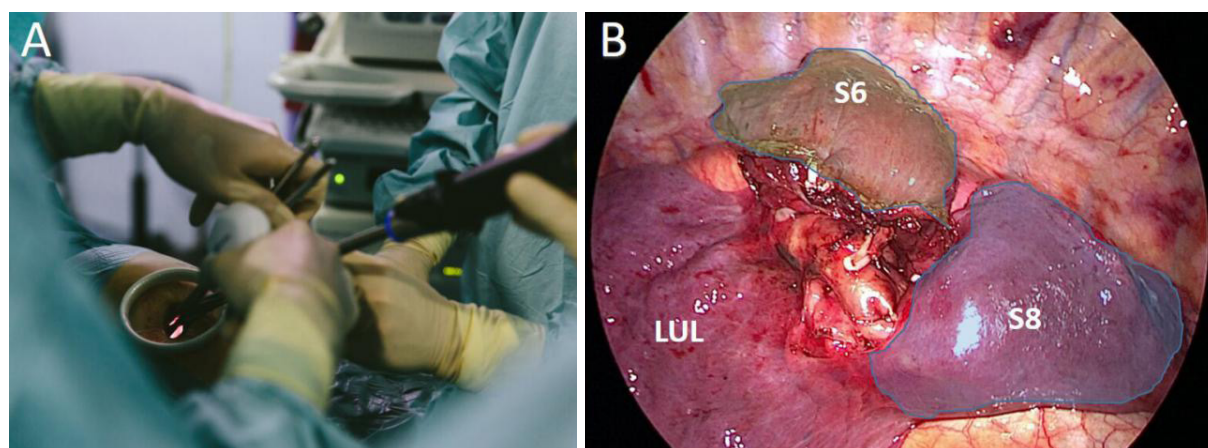


Figure 1. A: uniportal video-assisted thoracic surgery (VATS) instrumentation during left anatomical segmentectomy; B: preservation of left lower lobe S6 and S8 segments after S9+10 anatomical segmentectomy by uniportal VATS

THE ROLE OF SUBLOBAR RESECTION IN LUNG CANCER

Sublobar resections (SLR) include both non-anatomical wedge resections and anatomical resections of segments and subsegments with isolated division of both vascular and bronchial structures (i.e., anatomical segmentectomy). These procedures have specially spread within the last decade due to the diffusion and development of minimally invasive thoracic procedures, and the concept of “lung-sparing surgery”, which means preserving as much lung parenchyma as possible [Figure 1]^[5,21-24].

Main expected benefit of SLR when compared to lobectomy, is the preservation of higher amount of lung parenchyma, thus the absolute loss of postoperative lung function should be lower than for lobar and supralobar resections. This is why it has been considered an appropriate resection for compromised patients who cannot tolerate a standard lobectomy. Most published studies have not addressed the functional repercussion, but Charloux *et al.*^[25], in 2017, reported a lower decrease in postoperative forced expiratory volume at first second (FEV1) at 12 months in SLR compared to lobectomy (5% vs. 11%, respectively). They also reported lower decrease in global pulmonary function in patients with diminished preoperative lung function who undergone SLR, and a direct relationship between the number of resected segments and functional loss.

Anatomical segmentectomy has been used in the treatment of several pathologies, mainly benign lesions centrally located in the lobe, pulmonary metastasis, and early stage lung cancer^[26]. In the Lung Cancer Study Group report in 1995, SLR (i.e., anatomical and wedge) showed a higher recurrence and death rate in tumors less than 3 cm diameter, so lobectomy was set as the standard surgical treatment for early stage lung cancer^[3]. Since then, many studies have shown that anatomical SLR have comparable DFS and OS than lobectomy for tumors less than 2 cm^[4-8,21]. Thus, sublobar anatomical resections have been already included in main clinical guidelines (National Comprehensive Cancer Network -NCCN, European Society of Medical Oncology -ESMO) as an accepted procedure for early stage adenocarcinoma less than 2 cm, in peripheral location without nodal involvement, especially when ground-glass appearance or long duplication time have been observed^[27,28]. Most published studies are case series or comparative unicentric studies, so there is still a real lack of multicenter studies and randomized trials that specifically address these issues. Two prospective multicenter randomized trials are ongoing now comparing lobectomy to SLR: the Japanese Cooperative Oncological Group (JCOG) 0802 study was launched in Japan in 2009 to evaluate the overall survival of patients after segmentectomy and lobectomy for NSCLC^[29]. There are 71 centers where 1,100 individuals will be recruited. A similar study is pending in the USA (Cancer and Leukemia Group B

-CALGB- 140503) where 692 people are expected to be recruited^[30]. These two studies will probably clear some of the actual controversy and might set the indications for SLR in early stage NSCLC.

Studies comparing different approaches for sublobar resections have shown a shorter length of chest tube, shorter hospital stay, and less postoperative pulmonary complications in video-assisted thoracic surgery sublobar anatomical resections when compared to open thoracotomy^[26,31-33].

We must differentiate between two groups. The first group includes high-risk patients (FEV1 < 50%, diffusion capacity for carbon monoxide -DLCO < 50%) or combination of advanced age, impaired pulmonary function, pulmonary hypertension, or decreased left ventricle function^[34], where SLR and SABR are potential alternative therapeutic options to standard lobectomy. The second group includes elective intentional SLR in a specific subset of stage I NSCLC when compared to SABR.

COMPARISON OF SUBLOBAR RESECTION AND SABR IN NSCLC

Sublobar resection and SABR in high-risk or medically inoperable patients

There are very few studies that specifically address the results of sublobar resections compared to SABR in high-risk operable or medically inoperable lung cancer patients [Table 1]. When we consider this comparison, not only should oncological outcomes in terms of overall survival or loco-regional control be addressed, but also postoperative morbidity and mortality, patient's quality of life during and after treatment administration, and ability to deliver therapy (especially for SABR)^[41].

There are important factors that make these studies difficult that must be mentioned. First, the definition of local recurrence is usually different in surgical series than in SABR studies. Surgical series usually define local recurrence as recurrence in the staple line, in the chest wall, in the same lobe, or in the hilar or even mediastinal lymph nodes. On the other hand, SABR series define local recurrence only as recurrence in the primary tumor site^[41]. Second, patient population should be similar in both arms, because most SABR series have address only inoperable and high-risk operable patients who can die due to their comorbidities before a recurrence appears, while SLR have usually included both standard-risk and high risk operable patients. Third, adverse events should be homogenized because the chronological pattern of adverse events is different between these two therapeutic alternatives. While adverse events usually occur early in surgical patients, adverse events usually appear later in SABR patients. Fourth, in SABR patients, surgical nodal staging is usually not performed, especially when dealing with stage I tumors less than 2 cm in diameter^[35], so lymph node assessment is limited to pretreatment imaging studies (e.g., chest CT and PET scan).

Yendamuri *et al.*^[36], in 2007, retrospectively analyzed 160 clinical stage I NSCLC patients with contraindication for lobectomy (68 wedge resection and 92 3D conformal radiation therapy). They found a trend to better outcomes with limited resection with OS ($P = 0.010$) and recurrence-free survival (RFS) ($P = 0.000$) in the univariate analysis; however, that trend was only observed to be significant in the RFS in the multivariate analysis ($P = 0.002$). After a propensity matching score analysis, these differences in OS and RFS disappeared between both groups, so they concluded that both treatments were comparable.

In 2013, Mahmood *et al.*^[42] performed a Best Evidence Topic analysis comparing SABR with SLR in clinical stage I high-risk NSCLC patients. They only included 3 comparative studies. The first one^[37] found higher mean survival (4.1 years vs. 2.9 years) in the SLR group, and higher 4-year survival (51.3% vs. 30.1%). The second, Grills *et al.*^[38], reported higher rate of local recurrence with wedge resection compared to SABR (20% vs. 4%). OS was higher after wedge resection (87% vs. 72%; $P = 0.01$), but cause-specific survival showed no differences (94% vs. 93%; $P = 0.53$). In the third, Forquer *et al.*^[39] found no differences in 3-year survival were found, but they found higher median survival in SLR compared to SABR (55 months vs. 37 months), although no differences in cancer specific survival were observed. Dr. Scanagatta^[43] commented the

Table 1. Summary of comparative studies between SLR and SABR in high-risk or inoperable NSCLC

Author, year, country study type (level evidence)	Groups	Results	Comments
Yendamuri et al. ^[36] (2007) (USA) Retrospective observational study (level 3)	160 stage I NSCLC (contraindication for lobectomy) - 68 wedge resection - 92 3D conformal radiation therapy	Univariate analysis: - Better OS ($P = 0.010$) and RFS ($P = 0.000$) with wedge resection Multivariate analysis: - Better RFS ($P = 0.002$) Propensity score matching - No differences (OS $P =$ 0.609; RFS $P = 0.701$)	In high-risk patients with NSCLC, limited resection has a tendency towards improved outcome. Propensity matched analysis did not show a clear benefit for a wedge
Forquer et al. ^[39] (2007) (USA) Retrospective analysis	38 stage I NSCLC: - 19 SLR - 19 SBRT	3-year survival: - SLR - SBRT ($P = NS$) Median survival: - SLR 55 months - SBRT 37 months ($P = NS$) Cancer-specific deaths: - SLR 2/10 - SBRT 2/9	SLR and SBRT have similar survival results, although a trend towards better median survival in SLR
Grills et al. ^[38] (2010) (USA) Retrospective observational study (level 3)	124 T1-2N0 NSCLC: - 69 wedge resection - 58 SBRT	Local recurrence (LR): - wedge 20% - SBRT 4% ($P = 0.07$) Overall survival: - Wedge 87% - SBRT 72% ($P = 0.01$) Cancer specific survival (CSS): - Wedge 94% - SBRT 93% ($P = 0.53$)	SBRT and wedge resection are reasonable treatment options for Stage I NSCLC patients who are not suitable for lobectomy. Wedge resection has higher LR but higher OS. SBRT and surgery have comparable CSS
Puri et al. ^[37] (2012) (USA) Retrospective observational study (level 3)	114 stage I NSCLC: - 57 SLR - 57 SBRT	Median survival: - SLR: 4.1 years - SBRT: 2.9 years 4-year survival: - SLR: 51.4% - SBRT: 30.1% Cost - SLR \$17 629 - SBRT \$14 153	SLR is more cost-effective due to longer OS
Varlotto et al. ^[16] (2013) (USA) Retrospective study (databases)	317 NSCLC: - 48 wedge - 132 lobectomy - 137 SBRT	5-year OS: - SLR 86.3% - SBRT 31.7% ($P = 0.003$)	Better OS in wedge resection, but not significant in the multivariate analysis
Matsuo et al. ^[40] (2014) (Japan) Retrospective observational study (level 3)	180 stage I NSCLC (high-risk for lobectomy): - 65 SLR - 115 SBRT	5-year OS - SLR 55.6% - SBRT 40.4% ($P = 0.124$)	SBRT can be an alternative treatment option to SLR in high- risk patients who cannot tolerate lobectomy because of medical comorbidities
Ackerson et al. ^[9] (2018) (USA) Retrospective observational study (level 3)	221 stage I NSCLC: - 151 SLR (105 wedge and 46 segmentectomies) - 70 SBRT	3-year OS - SLR 63% - SBRT 35% ($P < 0.001$) 3-year DFS - SLR 42% - SBRT 29% ($P = 0.004$) Cancer-specific DFS - SLR 60% - SBRT 65% ($P = 0.84$). 3-year freedom from LR: - SLR 90% - SBRT 85% ($P = 0.71$). Complications/side effects: - SLR 23% - SABR 17%	SBRT and sublobar resection provide similar rates of local tumor control and overall clinical outcomes in stage I NSCLC

Tamura <i>et al.</i> ^[35] (2019) (Japan) Retrospective observational study (level 3)	247 stage I NSCLC with medical comorbidities:	5-year RFS:	SLR showed better RFS, with this difference significant in tumors > 2 cm in diameter. SBRT showed higher recurrence rate
	- 141 SLR (41 segmentectomies and 100 wedge) - 106 SBRT	- SLR 69.7% - SBRT 50.2% ($P = 0.036$) 5-year OS - SLR 75.2% - SBRT 70.2% ($P = 0.40$) Disease-specific survival (DSS) - SLR 89.5% - SBRT 76.0% ($P = 0.78$). 5-year RFS in > 2 cm: - SLR 69% - SBRT 32% ($P = 0.042$) Disease-specific survival (DSS) in > 2 cm - SLR 85.4% - SBRT 48.5% ($P = 0.064$). In < 2 cm: no differences in OS ($P = 0.81$), RFS ($P = 0.39$), DSS ($P = 0.89$) 5-year RFS in outer tumors: - SLR 72.1% - SBRT 42.2% ($P = 0.002$)	

NSCLC: non-small cell lung cancer; OS: overall survival; RFS: recurrence-free survival; SLR: sublobar resection; SABR: stereotactic ablative radiotherapy; SBRT: stereotactic body radiation therapy; DSS: disease-specific survival; CSS: cancer-specific survival; DFS: disease-free survival

potential benefit of the CyberKnife technology applied to SABR for these patients because it has a synchrony system for the respiratory movements with an accuracy of 2 mm or less, that might decrease collateral damage to surrounding parenchyma, as a potential issues for research.

Varlotta *et al.*^[16] reported, in 2013 from cancer databases, 48 SLR and 137 SABR patients with a median follow-up of 2.2 years. OS was superior in SLR compared with SABR matched pairs (86.3% and 31.7% for SLR and SABR at 5 years, respectively, $P = 0.003$). However, the multivariate analysis that included propensity scores as a covariate showed that the hazard ratio for OS was not significant, so no significant differences between both treatments could be drawn.

A retrospective analysis performed by Matsuo *et al.*^[40], in 2014, included patients with clinical stage I NSCLC at high-risk for lobectomy who underwent either SABR or SLR. After a propensity matching score analysis, there was no statistically significant difference in 5-year OS between both treatments (40.4% vs. 55.6%; $P = 0.124$).

Ackerson *et al.*^[9], in 2018, retrospectively compared 151 SLR (105 wedge and 46 segmentectomies) in clinical stage I patients not amenable to lobectomy, with 70 patients treated with SABR (89% deemed medically inoperable by surgeons due to severe decrease in pulmonary function or severe cardiovascular disease). Radiotherapy patients were older ($P = 0.019$), had higher Charlson comorbidity index score ($P < 0.001$), had lower pulmonary function in terms of FEV1 and DLCO ($P = 0.001$ and $P < 0.001$, respectively), and larger tumors ($P < 0.001$), making comparison problematic. OS and DFS were superior in the surgical group (3-year OS 63% vs. 35%, $P < 0.001$; 3-year DFS 42% vs. 29%, $P = 0.004$), but there were no differences in cancer-specific disease-free survival ($P = 0.84$). After adjusting for imbalances in baseline characteristics of both groups, there was no difference in overall survival between surgery and SABR (HR = 1.20; 95%CI: 0.74-1.95; $P = 0.46$). 3-year freedom from local recurrence was similar between both treatments (90% vs. 85%, $P = 0.71$). In the surgical group, 23% developed postoperative complications, while in the SABR group there were complications in 17%.

A retrospective study of Tamura *et al.*^[35], in 2019, compared 106 SABR patients with 141 SLR (100 wedge and 41 anatomical segmentectomies) in clinical stage I NSCLC with medical comorbidities (e.g., poor

pulmonary function, chronic lung disease, old age, and poor performance status). The 5-year RFS was higher in the SLR group (69.7% *vs.* 50.2%; $P = 0.036$), but there were no statistically differences in OS (75.2% *vs.* 70.2%; $P = 0.40$) or in disease-specific survival (89.5% *vs.* 76.0%; $P = 0.78$). In tumors larger than 2 cm in diameter, RFS and disease-specific survival were higher in the SLR group, while in tumors less than 2 cm in diameter there were no differences in OS, RFS, or disease-specific survival. Local recurrence rate was higher in the SABR group ($P = 0.0082$) in tumors located in the outer third of lung parenchyma, while no significant difference could be seen in the internal group. Regional recurrence and distant metastasis rate showed no differences between both groups.

None of these studies was randomized, so the evidence is limited, but it seems that in these compromised patients, both treatments show similar overall survival, with a trend to better local control in surgical patients, especially with tumors larger than 2 cm or in the outer third of the lung.

The SABRTooth trial was a UK multi-center, randomized controlled feasibility study targeting patients with peripheral stage I NSCLC considered to be at higher risk of surgical complications. They planned to randomize 54 patients 1:1 to SABR or surgery. Between July 2015 and January 2017, 318 patients were considered for the study but only 106 assessed as eligible (33.3%), from whom 24 patients (22.6%) were randomized to SABR ($n = 14$) or surgery ($n = 10$). The main reason for nonparticipation was treatment preference with 43 (41%) preferring non-surgical treatment and 19 (18%) preferring surgery. The average monthly recruitment rate was 1.7 patients against an initial target of 3. Only 15 patients underwent their allocated treatment, 12 SABR and 3 surgery, proving the difficulty of setting a randomized trial in this high-risk population^[44].

Sublobar resection and SABR in operable stage I NSCLC

Despite lobectomy still being the standard treatment for early stage lung cancer^[28,45], sublobar resections, mainly anatomical segmentectomy, have progressively increased for treating stage I NSCLC less than 2 cm without nodal involvement due to similar oncological outcomes in terms of local control and overall survival^[4-8]. Sometimes, patients refuse surgical treatment due to personal concerns or frightens when facing the postoperative risks, so SABR is the most common alternative offered in these situations. It has shown optimal local control (92% 5-year local progression-free rate in stage IA, and 73% in stage IB) and acceptable 5-year overall survival rates (72% in stage IA, and 63.2% in stage IB^[46]). But which are the comparative results of these treatments in those stage I patients where SLR can be offered?

A meta-analysis was published in 2017 comparing surgery (i.e., lobectomy and SLR) with SABR in stage I NSCLC^[47]. No randomized trial was included, but 12 cohort studies, with more than 13,000 patients. SABR showed worse outcomes in terms of 3-year survival (RR = 0.78; $P = 0.001$) and OS (HR = 1.60; $P < 0.001$), but when a subgroup analysis was performed comparing SLR with SABR (4 of 12 studies), there were no significant differences in terms of 3-year survival, OS, and 3-year locoregional control. This meta-analysis did not distinguish between wedge or anatomical segmentectomy, and also included studies dealing with the elderly or high-risk patients, so this heterogeneity highlights the need for careful conclusions.

Chen *et al.*^[48] published another meta-analysis of 16 propensity score studies including more than 19,000 patients. Results favored SLR compared to SABR (HR = 1.28; 95% CI: 1.06-1.56) in terms of OS, but there were no statistical differences in terms of lung cancer specific survival (HR = 1.22; 95% CI: 0.95-1.57). There was also no distinction between wedge and anatomical segmentectomy, and the meta-analysis also included comparative studies in the elderly or high-risk surgical patients.

Iguchi *et al.*^[49] published a single-center retrospective evaluation of the results of 3 modalities in stage I NSCLC (i.e., radiofrequency ablation, SABR, and SLR). SLR has achieved longer survival, but after adjustment, only reduce HR of disease progression and death of any cause were observed ($P = 0.038$).

A retrospective analysis of 4,069 US veterans by Bryant *et al.*^[50], with 449 SABR and 634 SLR (414 wedge and 220 anatomical segmentectomies), found no statistical differences in cancer-specific survival (HR = 1.25; 95%CI: 0.93-1.68; $P = 0.15$) or OS (HR = 1.17; 95%CI: 0.90-1.53; $P = 0.85$) between both treatments, while lobectomy was superior to SABR.

A National Cancer Database study was conducted by Wu *et al.*^[51]. After propensity score matching, 9,967 patients treated by SABR resulted in shorter OS compared to 9,967 SLR patients. Both wedge resection and anatomical segmentectomy showed longer OS, whereas segmentectomy patients had longer median survival than wedge patients (71.4 years vs. 58.0 years; $P < 0.001$). In tumors less than 2 cm in diameter, SABR had higher hazard of mortality than SLR ($P < 0.001$).

A meta-analysis by Cao *et al.*^[7], in 2019, compared SABR and surgery in NSCLC. There was no limitation to early stage NSCLC, and no subgroup analysis in stage I. In the subgroup analysis of sublobar resections, OS was superior in SLR compared to SABR in unmatched patients from 6 studies (OR = 1.54; 95%CI: 1.36-1.75; $P < 0.00001$), but there were insufficient matched patients to perform a meta-analysis. All these studies are summarized in Table 2.

There is one randomized trial in course, the VALOR trial (NCT02984761), comparing anatomical pulmonary resection (lobectomy and segmentectomy) with SABR in stage I biopsy-proven NSCLC. The estimated accrual is 670 patients and the primary endpoint is 5-year OS, and the expected completion date is 2027.

Guidelines of the American Society of Radiation Oncology^[52] do not recommend SABR out of a clinical trial in patients with standard operative risk for lobectomy with systematic lymph node dissection. But as many recent studies advocate for lung-preserving SLR in early stages, the question that remarks unanswered is: In those cases, does SABR constitutes an alternative treatment due to better toxicity profile? Or does the advantages of a surgical exploration (e.g., visualization of cavity and other lobes, lymph node assessment, and resection of primary lesion) makes SLR the optimal treatment?

Sublobar resection and SABR in nodules detected during lung cancer screening tests

The National Lung Screening Trial (NLST)^[53] found that 68% of NSCLC rightly diagnosed by CT were stage I^[12], and reported a 20% decrease in lung cancer specific mortality ($P = 0.004$) and 6.7% in overall mortality ($P = 0.02$) compared to the radiography group. Several other lung screening trials have supported these results^[54]. But not all these newly diagnosed small nodules are malignancies, so it raises the controversy of how to deal with these nodules. Surgical resection offers the possibility of assessing hilar and mediastinal lymph nodes (20% occult nodal metastasis in clinical stage I^[12,55], although lower in screening-detected tumors^[56]), and also obtains a complete nodule resection for assessing pathological prognostic factors. Other potential disadvantages of SABR when compared to surgery are the overtreatment of false positive lesions, and the fact that nodules are not resected, so follow-up implies the careful performance and analysis of residual scar lesions and their potential growth^[55].

An issue that makes SABR an attractive alternative in screening detected tumors is the toxicity profile, which seems to be less severe for SABR. Also, a mean 30-day mortality of 10% in severe chronic obstructive pulmonary disease stage I NSCLC after surgery makes a less toxic algorithm appear as a desirable option^[57].

For peripheral screen detected early stage NSCLC in patients amenable to surgery, this seems the most suitable option because it also offers accurate staging, definitive diagnosis, and pathological prognostic factors assessment^[55]. In patients at high-risk for surgery or patients who are inoperable, SABR should be offered to patients in a shared decision-making process as it provides similar disease control with better

Table 2. Summary of comparative studies between SLR and SABR including operable NSCLC

Author, year, country Study type (level evidence)	Groups	Results	Comments
Deng et al. ^[47] (2017) (China) Meta-analysis (level evidence 1)	13,598 stage I NSCLC three strategies (SBRT, SLR, lobectomy) 12 cohort studies (4 studies comparative with SLR) No randomized trial	3 year survival rate: - SABR worse than SLR (RR = 0.78; $P = 0.001$) OS: - SABR worse than SLR (HR = 1.60; $P < 0.001$) Subgroup analysis (4 of 12 studies), there were no significant differences in terms of 3-year survival, OS and 3-year locoregional control	SABR shows a local control rate comparable to that of lobectomy and sublobar resection In patients not amenable to lobectomy, SABR is an alternative treatment comparable to sublobar resection
Chen et al. ^[48] (2018) (Canada) Meta-analysis (level evidence 1)	19,882 patients 16 propensity score studies No randomized trial	OS: - SABR worse than SLR (HR = 1.28; 95%CI: 1.06-1.56) Lung cancer specific survival: - No differences (HR = 1.22; 95%CI: 0.95-1.57)	Better OS with SLR but the meta-analysis included studies of patients at risk for surgery. No distinction between wedge and segmentectomy
Iguchi et al. ^[49] (2020) (Japan) Retrospective observational study (level 3)	289 patients stage I NSCLC: - 38 RF ablation - 58 SBRT - 193 SLR	5 year overall survival (OS): - 58.9% RF ablation - 42% SBRT - 85.5% SLR 5 year progression free survival (PFS): - 39.9% RF ablation - 34.9% SBRT - 75.9% SLR After propensity score: 5 year overall survival (OS): - 59.7% RF ablation - 63.7% SBRT - 71% SLR 5 year progression free survival (PFS): - 35.9% RF ablation - 55.7% SBRT - 61.9% SLR	SLR shows a trend towards longer survival, but SBRT can be an alternative in stage I NSCLC
Bryant et al. ^[50] (2018) (USA) Retrospective observational study (level 3)	1,083 early stage NSCLC: - 634 SLR - 449 SBRT	Cancer-specific survival (CSS): - No differences (HR = 1.25; 95%CI: 0.93-1.68; $P = 0.15$) Overall survival (OS): - No differences (HR 1.17; 95%CI: 0.90-1.53; $P = 0.85$)	Lobectomy improves survival comparing to SBRT in early stage NSCLC, while there are no differences between SLR and SBRT
Wu et al. ^[51] (2020) (China) Retrospective study (databases)	19,934 NSCLC: - 9,967 SLR - 9,967 SBRT	Overall survival (OS): - SLR 60.4 months - SBRT 40.5 months (HR = 1.559; 95%CI: 1.497-1.623; $P < 0.001$) Median survival: - Segmentectomy 71.4 months - Wedge 58.0 months ($P < 0.001$) Tumors ≤ 2 cm: - SBRT median 45.0 months - SLR 67.5 months (HR = 1.626; 95%CI: 1.538-1.720; $P < 0.001$)	SLR may be associated with increased survival in patients with stage I NSCLC compared with SBRT Other variables such as cardiopulmonary function probably play a role in treatment selection and may affect survival
Cao et al. ^[7] (2019) (USA) Meta-analysis (level evidence 1)	23 studies in NSCLC	Overall survival: - higher in SLR than SABR in unmatched patients from 6 studies (OR = 1.54; 95%CI: 1.36-1.75; $P < 0.00001$)	Surgery might be superior to SBRT in terms of mid- and long-term clinical outcomes SBRT is associated with lower perioperative mortality Improved outcomes after surgery, may be attributable at least in part to an imbalance of baseline characteristics

NSCLC: non-small cell lung cancer; OS: overall survival; RFS: recurrence-free survival; SLR: sublobar resection; SABR: stereotactic ablative radiotherapy; SBRT: stereotactic body radiation therapy; DSS: disease-specific survival; CSS: cancer-specific survival

safety profile, although the evidence is limited by the absence of randomized trials in this specific subset of patients. A multidisciplinary assessment in a tumor board with different professionals should guide the individual decision-making process.

QUESTIONS THAT REMAIN UNANSWERED

Some important topics should be investigated with emphasis to achieve quality levels of evidence in order to set the role of SLR and SABR in NSCLC treatment algorithms:

- Is SLR really an alternative to lobectomy in early stage NSCLC, and if so, which is its exact indications (e.g. tumor size, margin to tumor ratio, histological types and subtypes, radiological pattern, nodal assessment)?
- What is the role of wedge resection in stage I NSCLC and which patients benefit?
- Is SABR a real alternative to limited resection in patients with stage I NSCLC at high-risk for surgery?
- Should SABR be offered in operable stage I NSCLC now that minimally-invasive surgery and SLR are available?
- Regarding the limitations of SABR in nodal staging and the difficulties in surveillance of post-radiation lung scars, does patient age play a role in offering SABR during the decision-making process?

CONCLUSION

High-quality multicenter and randomized studies comparing SLR with SABR in NSCLC treatment are missing. Retrospective and prospective comparative studies and series, and some meta-analysis or propensity score matching studies show that SABR is a potential alternative treatment for in stage I NSCLC patients. A trend towards better survival and local control has been found with SLR, but lower adverse effects profile makes SABR an attractive alternative, especially when dealing with patients at high-risk or inoperable stage I NSCLC, so it should be included in the decision-making process.

DECLARATIONS

Authors' contributions

Review and writing: Galvez C

Conception and design of the study: Galvez C, Bolufer S, Corcoles JM, Lirio F, Sesma J, Mafe JJ, Cerezal J

Availability of data and materials

Not applicable.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Meta-Analysis

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A systematic review and meta-analysis comparing intracorporeal anastomosis and extracorporeal anastomosis in minimally invasive colectomies

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Abstract

Aim: This systemic review aims to determine if intracorporeal anastomosis (IA) adds value to patient outcomes without compromising operative and oncological safety when compared to extracorporeal anastomosis (EA) in laparoscopic colectomies. This is the first systematic review with meta-analysis to evaluate the outcomes in a combined fashion including both laparoscopic right and left colectomies.

Methods: A systematic review of Medline, EMBASE, Cochrane Library, and PubMed was performed on studies analysing direct comparison between IA and EA. The primary outcome was anastomotic leakage. Quality assessment was carried out using a modified Institute of Health Economics appraisal tool. Meta-analysis was performed using a random-effects model.

Results: A total of 24 papers with 2,674 patients were included in the analysis. No significant difference was found in anastomotic leakage (OR = 0.84; 95%CI: 0.54-1.31; $P = 0.44$) and short-term mortality (OR = 0.56; 95%CI: 0.20-1.58; $P = 0.27$) between the IA and EA cohorts. The IA cohort was associated with faster return of bowel function [MD = -0.53 days; 95%CI: -0.67-(-0.39); $P < 0.00001$] and lower incidence of surgical site infection



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(OR = 0.52; 95%CI: 0.31-0.85; $P = 0.009$). The number of lymph nodes harvested was higher in IA (MD = 1.05; 95%CI: 0.19-1.91; $P = 0.02$; $I^2 = 83\%$) with considerable heterogeneity.

Conclusion: Intracorporeal anastomosis can be considered a safe alternative technique in laparoscopic colectomies, with potential benefits in patient outcomes. A lack of randomised studies and heterogeneity need to be addressed by additional high-quality trials.

Keywords: Laparoscopic, intracorporeal, extracorporeal, colectomy, outcome

INTRODUCTION

Laparoscopic colectomy has been increasingly performed worldwide since its introduction and it is currently considered the “gold standard” surgical care for benign and malignant colon resections^[1]. The most common indication for the colon resection is malignancy, which is the second leading cause of cancer death worldwide, with a lifetime incidence of approximately 6%^[2].

In general, the term “laparoscopic colectomy” refers to laparoscopic-assisted colectomy with extracorporeal anastomosis (EA). Extracorporeal anastomosis is the preferred technique as intracorporeal anastomosis (IA) is considered more technically challenging due to the need for laparoscopic suturing and the potential risk of intra-abdominal spillage^[3,4]. Subsequently, there has been concern about a greater likelihood of anastomotic leak^[5]. However, IA is less invasive, and there is accumulating data to support its safety and potential short-term benefits in the post-operative period^[6,7]. Unfortunately, available meta-analyses are limited to right colectomies based on limited observational studies while there is a paucity of data on left colectomies.

Traditionally, left colectomy is perceived to be more challenging than right colectomy due to the need for extensive posterior dissection during mobilisation of the splenic flexure and its anatomic characteristics of multiple lymphatic drainage. However, a study by Iorio *et al.*^[8], investigating direct comparison of surgical outcomes in laparoscopic IA approach between right-sided and left-sided tumours, concluded that the location of the tumour itself did not have significant impact on patient clinical outcome, including anastomotic leakage.

The aim of this study was, therefore, to conduct a comprehensive systematic review to perform a combined meta-analysis of left and right-sided colectomies in order to broaden the existing understanding on the safety and potential benefits of IA in laparoscopic colectomy, irrespective of its primary location.

METHODS

Study design

Literature search and data extraction

A systematic literature search was carried out by two independent researchers using electronic databases including Medline, EMBASE, Cochrane Library, and PubMed. The following search strategy was used for database extraction using Endnote (Version X8, Clarivate Analytics®): “intracorporeal” OR “extracorporeal” OR “anastomosis” OR “laparoscopic assisted” OR “totally laparoscopic” AND “colectomy” and (“laparoscopy” or “laparoscopic”). The search was performed without any restriction on language or publication status. Studies published in a language other than English were excluded unless its full article was available in an English edition.

Inclusion and exclusion criteria

The following inclusion criteria were prerequisite to be included in the meta-analysis: (1) direct comparison of the pre-determined outcomes of IA with EA involving right-sided and/or left-sided colectomies; and (2) reported data concerning at least the primary endpoint (i.e., anastomotic leakage). If two studies were reported by the same institution and/or authors, the one with more comprehensive data was included, unless the studies were of different design and encompassed distinctive study population.

Non-comparative studies such as case series, description of particular techniques, along with animal studies, conference abstracts, review articles, opinions and editorials were excluded from the analysis. Furthermore, studies with inadequate data or that described other types of resections (e.g., single-incision approach, purely robotic, sub-total colectomy, primary rectosigmoid resection, and palliative resection) were excluded as well. The natural orifice extraction studies were excluded as it is currently not a widely practiced method and its validity is still to be confirmed^[9].

Outcome measures

The primary endpoint was anastomotic leakage since the safety of a surgical technique is considered the most vital. An anastomotic leak was defined as a defect in the intestinal wall integrity at the anastomotic site leading to a communication between the intraluminal and extraluminal compartments either clinically or radiologically^[10].

With regard to the secondary outcomes, we chose the following clinical endpoints to best reflect crucial clinical consequences of colonic resection:

Intraoperative:

- (1) Operative time
- (2) Number of lymph nodes harvested

Post-operative:

- (1) Mortality, defined as any deaths occurred during hospitalisation or within 30 days post-operatively
- (2) Need for re-intervention
- (3) Time to first flatus
- (4) Surgical site infections
- (5) Incidence of post-operative incisional hernia

Data analysis

Statistical analysis

The meta-analysis was performed using Review Manager 5.3 (Cochrane Community) and was conducted in accordance with recommendations from the Cochrane Collaboration and Meta-Analysis of Observational Studies in Epidemiology Guidelines.

The statistical analysis for dichotomous variables was summarised by calculating odds ratios (OR) with a confidence interval (CI) of 95%. Mantel-Haenszel method was used to calculate the effect size by combining the odds ratios of the outcomes using a random-effects model. Odds ratio < 1 favoured the IA group while odds ratio > 1 favoured the EA group. This was considered statistically significant if $P < 0.05$ and if the confidence interval did not include 1. Continuous variables were statistically analysed by calculating the weighted mean difference (WMD) with a 95% confidence interval. A positive WMD indicated that the pooled mean value of the outcome was higher in the IA group and was considered statistically significant if $P < 0.05$. Study heterogeneity was evaluated using I^2 statistics. $I^2 > 50\%$ was considered substantial (i.e., serious heterogeneity) while $I^2 < 50\%$ was considered low-moderate risk of heterogeneity. In studies which

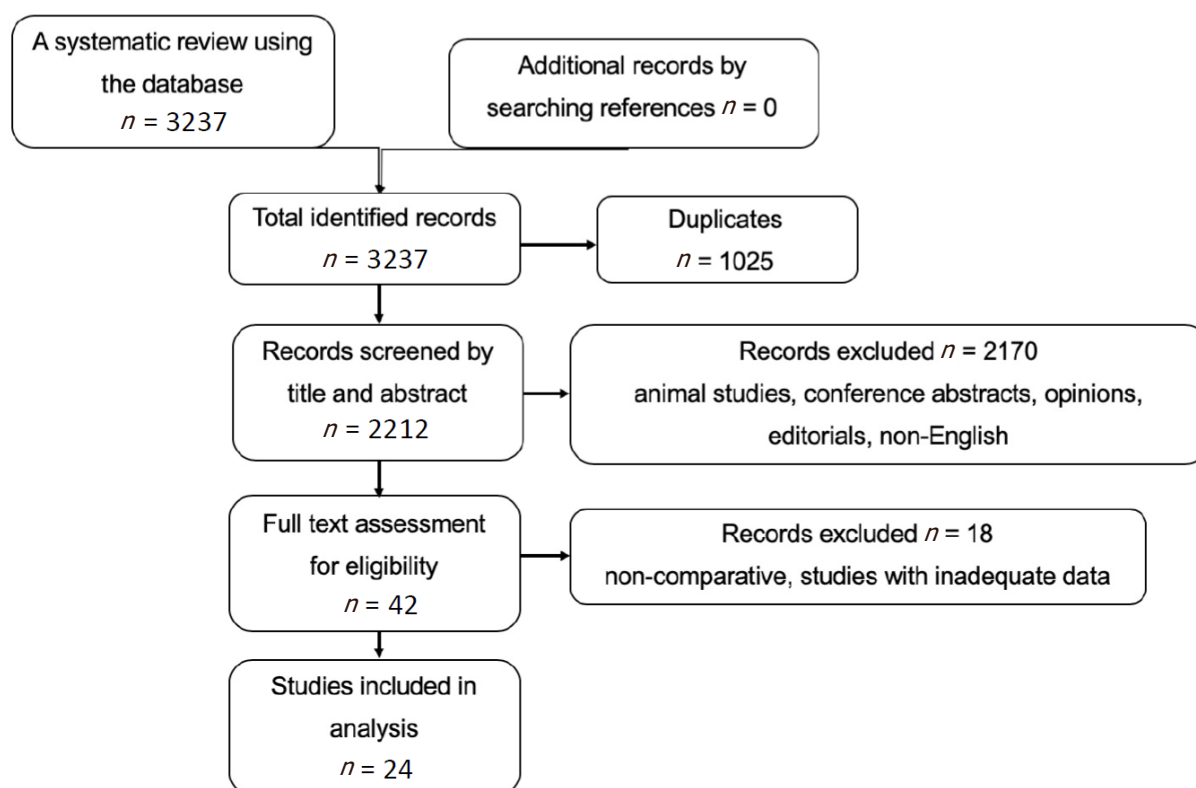


Figure 1. PRISMA flowchart for the systematic review of literature

included median with range, a dedicated mathematical conversion to mean and standard deviation was carried out using methods from Wan *et al.*^[11].

Forest plots were constructed for meta-analysis on pre-determined outcomes by evaluating the total colectomies combined. A meta regression analysis and leave-one-out analysis were performed for the primary outcome to identify potential heterogeneity. Publication bias was assessed using Begg's and Egger's test.

RESULTS

Included articles

The flow chart on search results of the literature in accordance with the PRISMA statement are displayed in [Figure 1](#). The search identified a total number of 3,237 potential articles published between 1991 and 2019. A total of 42 articles met initial inclusion criteria and full-text articles were reviewed. After thorough process of literature review and discussion between two independent reviewers, 24 papers were determined to be eligible for data extraction and subsequent statistical analysis. Cross-checking of all references of the included papers did not identify any additional studies.

The included studies for final analysis resulted in a total of 2,674 patients who had undergone laparoscopic colectomy. This was split into 1,412 patients (52.8%) in the intervention group (i.e., intracorporeal anastomosis) and 1,262 (47.2%) in the control group (i.e., extracorporeal anastomosis). The study design and characteristics of each study included are described in [Table 1](#).

Two papers were identified to have been published by the same author, Vignali *et al.*^[12,13]. After a thorough review, both studies were considered for inclusion in our analysis as they were of different study design, with Vignali *et al.*^[12] evaluating the outcomes in a specific patient cohort, the obese population, as evident

Table 1. Study characteristics and demographic data

	Year	Recruitment	Country	Study design	Location	IA (n)	EA (n)	Multi-centre	IHE quality score	Age (IA)	Age (EA)	BMI (IA)	BMI (EA)	Malignant (IA)	Malignant (EA)	Anastomosis
Allaix et al. ^[14]	2019	2017-2018	Italy	Double-blind randomised	Right	70	70	N		70.5 ± 3	71.5 ± 3	24.8 ± 1.6	25.6 ± 1.6	77.1%	87.1%	Side-to-Side Linear Stapler for IA; Variations in EA
Anania et al. ^[15]	2012	2006-2010	Italy	Retrospective	Right	39	33	N	23	74.5 ± 9	74 ± 12	27.4 ± 4.3	28.3 ± 4.3	64.1%	84.8%	Side-to-Side Linear Stapler
Biondi et al. ^[16]	2017	2006-2016	Italy	Retrospective	Right	54	54	N	22	69.5 ± 12.7	68.6 ± 9.8	25.6 ± 4.7	26.3 ± 3.2	88.9%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Chaves et al. ^[17]	2011	2004-2010	Spain	Retrospective	Right	35	25	N	24	62.2 ± 13.4	58.9 ± 12.9	25.9 ± 3.1	26.7 ± 3.9	62.9%	72%	Side-to-Side Linear Stapler; Isoperistaltic
Jian-Cheng et al. ^[18]	2016	2011-2015	China	Retrospective	Right	56	29	N	22	68 ± 8.3	69 ± 6.5	20.3 ± 2	20.6 ± 1.7	NR	NR	Linear Stapler
Erguner et al. ^[19]	2013	NR	Turkey	Retrospective	Right	15	15	N	23	65.4 ± 9.6	63.3 ± 13	27 ± 3.5	25.8 ± 3.2	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Fabozzi et al. ^[20]	2010	2001-2009	Italy	Retrospective	Right	50	50	N	21	62.1 ± 8.3	59.4 ± 9.5	21.4 ± 2.3	22.1 ± 1.6	100%	100%	Linear Stapler; Isoperistaltic
Franklin et al. ^[21]	2004	1991-2002	USA	Retrospective	Right	82	10	N	24	NR	NR	NR	NR	100%	100%	Linear Stapler
Grams et al. ^[22]	2010	2006-2008	USA	Retrospective	Right	54	51	N	22	45	50	23.8	23.4	24.1%	29.4%	Side-to-Side Linear or Circular Stapler
Hanna et al. ^[23]	2015	2005-2014	USA	Retrospective	Right	86	109	Y	27	66 ± 4	59 ± 4.5	26.1 ± 1.1	25.5 ± 1.4	82.6%	65.1%	Side-to-Side Linear Stapler; Isoperistaltic
Hellan et al. ^[24]	2009	2004-2008	USA	Retrospective	Right	23	57	N	25	65.8 ± 8.8	66.5 ± 14	28.8 ± 5.3	28.5 ± 5	65.2%	63.2%	Side-to-Side Linear Stapler
Lee et al. ^[25]	2013	2005-2010	USA	Retrospective	Right	51	35	Y	27	70 ± 11.8	66 ± 11.3	29 ± 7.1	28.6 ± 6.8	100%	100%	Side-to-Side Linear Stapler; Anti-peristaltic
Magistro et al. ^[26]	2013	2009-2011	Italy	Prospective	Right	40	40	N	25	70.9 ± 13.4	71.2 ± 10.5	24.8 ± 2.8	23.9 ± 4.4	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Marchesi et al. ^[27]	2013	2006-2010	Italy	Retrospective	Right	28	27	N	24	66.2	67.7	26.1	26.2	60.7%	63%	Side-to-Side Linear Stapler; Isoperistaltic
Mari et al. ^[28]	2018	2015-2016	Italy	Prospective randomised	Right	30	30	N		64.3 ± 10.3	65 ± 14.5	24.3 ± 5.9	26.1 ± 3.3	NR	NR	Linear Stapler
Milone et al. ^[29]	2015	2005-2012	Italy	Prospective	Right	286	226	Y	28	66.7 ± 12.6	65.6 ± 11.4	25.2 ± 3.8	25.4 ± 3.8	100%	100%	Side-to-Side Linear Stapler
Milone et al. ^[29]	2018	2005-2015	Italy	Retrospective	Left	92	89	Y	28	66 ± 10.9	68.7 ± 10.2	29.5 ± 4.3	24.7 ± 4.2	100%	100%	Side-to-Side Linear Stapler
Roscio et al. ^[30]	2012	2006-2011	Italy	Retrospective	Right	42	30	N	25	63.5 ± 10.3	63.7 ± 10.3	26 ± 4	26.3 ± 3.8	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Scatizzi et al. ^[31]	2010	2006-2009	Italy	Retrospective	Right	40	40	N	24	65.7 ± 11	68.5 ± 10	27	28	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Shapiro et al. ^[32]	2016	2006-2014	Israel	Prospective	Right	91	100	Y	26	72 ± 7.5	72 ± 6.8	27.8 ± 4.6	26.9 ± 4.3	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Swaid et al. ^[33]	2016	2005-2014	Israel	Retrospective	Left	33	19	N	22	64.2 ± 12.4	72.7 ± 2.1	25.4 ± 3.9	25 ± 3.6	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Vergis et al. ^[34]	2015	2008-2009	Canada	Retrospective	Right	21	29	N	22	65	69	21.7	28.6	NR	NR	Side-to-Side Linear Stapler
Vignali et al. ^[13]	2016	2008-2015	Italy	Prospective randomised	Right	30	30	N		67.4 ± 1.8	64.7 ± 2.9	24.6 ± 4.3	24.8 ± 3.4	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Vignali et al. ^[12]	2018	2008-2015	Italy	Retrospective	Right	64	64	N	24	61.3 ± 13.3	63.5 ± 13.5	31.4 ± 2	31.6 ± 2.2	82.8%	85.9%	Side-to-Side Linear Stapler; Isoperistaltic

IA: intracorporeal anastomosis; EA: extracorporeal anastomosis; BMI: body mass index; IHE: Institute of Health Economics

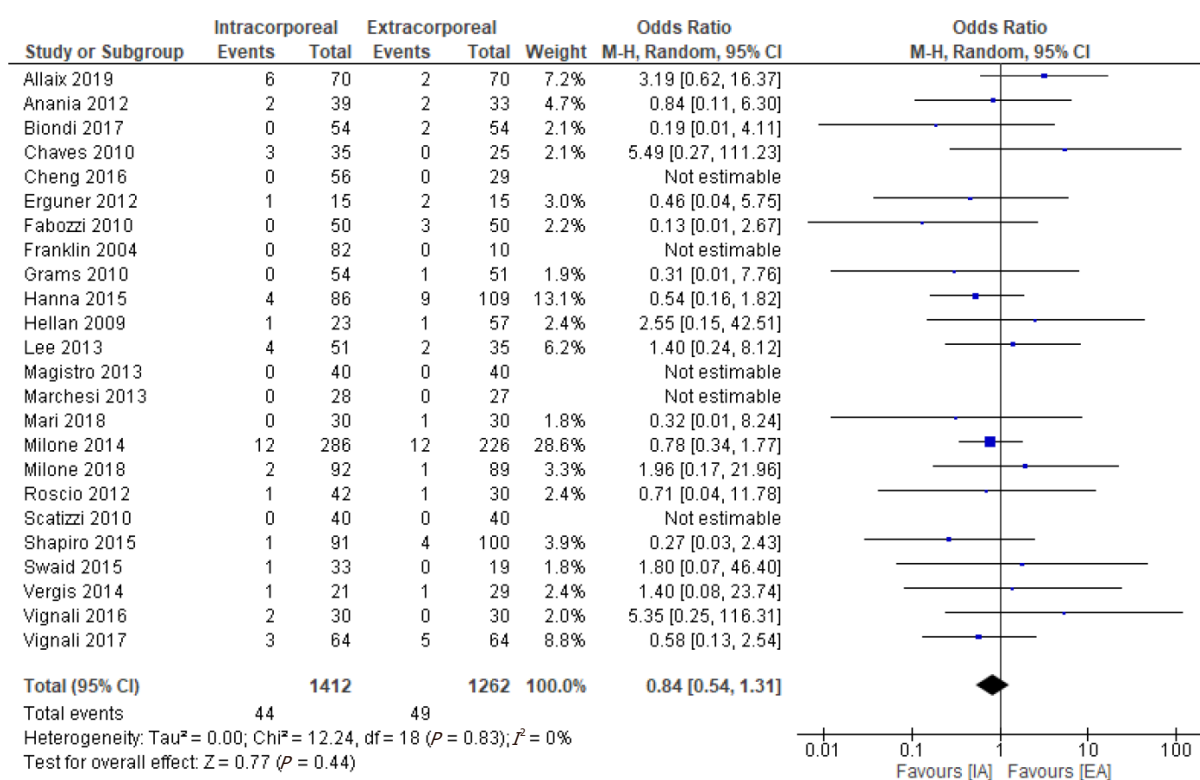


Figure 2. Meta-analysis of anastomotic leakage

by the significant difference in average body mass index (BMI) of the patient cohort included in the study [Table 1]^[12].

Study characteristics and demographic data

The surgical technique used to perform IA anastomosis was similar in all included studies. A mechanical linear stapler was the method of choice for bowel anastomosis for both intracorporeal and extracorporeal approach, reported in all 24 articles. However, a large variation was noted among published literature for the closure of enterotomies and the length of anastomosis.

The overall mean age, reported in twenty-three articles, was 65.7 years in the IA group and 66.0 years in the EA group. The male to female ratio was 1.1:1 for IA cohort and 1:1 for the EA. The average BMI, reported in 23 papers, was 25.8 kg/m² for the IA cohort and 26.0 kg/m² for the EA group.

Quality assessment: modified Institute of Health Economics quality appraisal tool

The modified Institute of Health Economics (IHE) quality appraisal tool used is displayed in Supplement Table 1^[35]. The assessment was conducted for 21 comparative, non-randomised studies. The mean score was 24.2 (range 21-28) out of a total of 30 points. Study with a score ≥ 26 was considered of high quality.

Meta-analysis

Primary outcome

Anastomotic Leakage: The overall rate of anastomotic leakage [Figure 2] reported in 24 articles was 3.1% (44 cases) for the IA and 3.9% (49 cases) for the EA. The meta-analysis did not reveal a statistically significant difference (OR = 0.84; 95%CI: 0.54-1.31; $P = 0.44$; $I^2 = 0\%$).

Secondary outcomes

Operative time: The operative time [Figure 3] was reported in 21 studies. It was 10 min longer for IA (MD = 9.99 min; 95%CI: 3.68-16.31; $P = 0.002$; $I^2 = 85\%$), which was statistically significant.

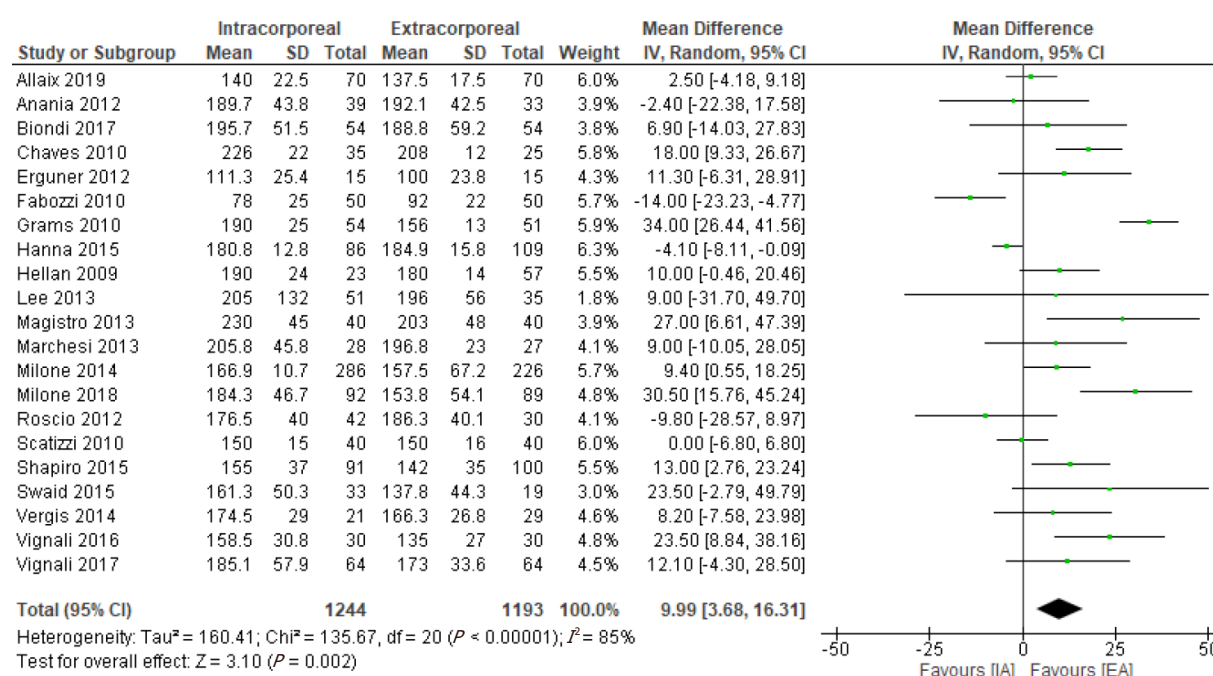


Figure 3. Meta-analysis of operative time

Lymph node harvesting: The number of lymph nodes harvested [Figure 4] in oncological resections was documented in 19 studies. Meta-analysis demonstrated that IA was associated with higher number of lymph nodes harvested (MD = 1.05; 95%CI: 0.19-1.91; $P = 0.02$; $I^2 = 83\%$). This was statistically significant but with considerable heterogeneity.

Mortality: Mortality was reported in 22 studies [Figure 5]. There were 3 deaths in the IA group and 8 in the EA group. No statistically significant difference was observed between the two groups (OR = 0.56; 95%CI: 0.20-1.58; $P = 0.27$; $I^2 = 0\%$).

Post-operative surgical complications: The indicators of post-operative complications were comprised of the incidence of surgical site infection, incisional hernia, and the need for re-intervention.

Post-operative surgical site infection [Figure 6] was investigated in 20 studies. The rate of post-operative wound infection was 3.7% (46 cases) in IA and 7.7% (90 cases) in EA. The incidence of post-operative incisional hernia [Figure 7] was evaluated in 12 articles, and the rate of incisional hernia development was 2.8% (17 cases) in IA and 10.9% (67 cases) in EA. Meta-analysis demonstrated that the incidence of surgical site infection (OR = 0.52; 95%CI: 0.31-0.85; $P = 0.009$; $I^2 = 27\%$) and incisional hernia (OR = 0.30; 95%CI: 0.17-0.53; $P < 0.0001$; $I^2 = 0\%$) was significantly lower in IA group.

The need for re-intervention [Figure 8] demonstrated no statistically significant difference between the two groups (OR = 0.72; 95%CI: 0.45-1.16; $P = 0.18$; $I^2 = 0\%$).

Return of bowel function outcomes: Time to first flatus was reported in 13 studies [Figure 9]. The analysis demonstrated that the patients in IA group had faster return to gut function as measured by first flatus [MD = -0.53 days; 95%CI: -0.67-(-0.39); $P < 0.00001$; $I^2 = 56\%$].

Heterogeneity: The heterogeneity was low for the primary endpoint (i.e., $I^2 = 0$ for anastomotic leakage). However, it was variable for the secondary outcomes. The heterogeneity was low for mortality, surgical

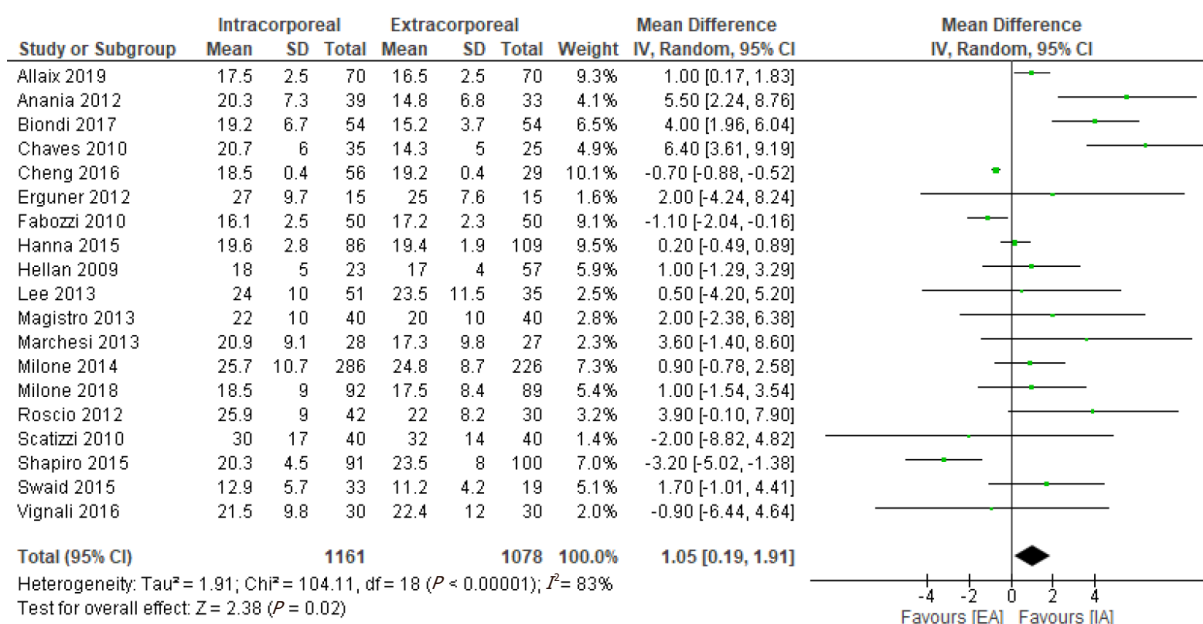


Figure 4. Meta-analysis of lymph node harvesting

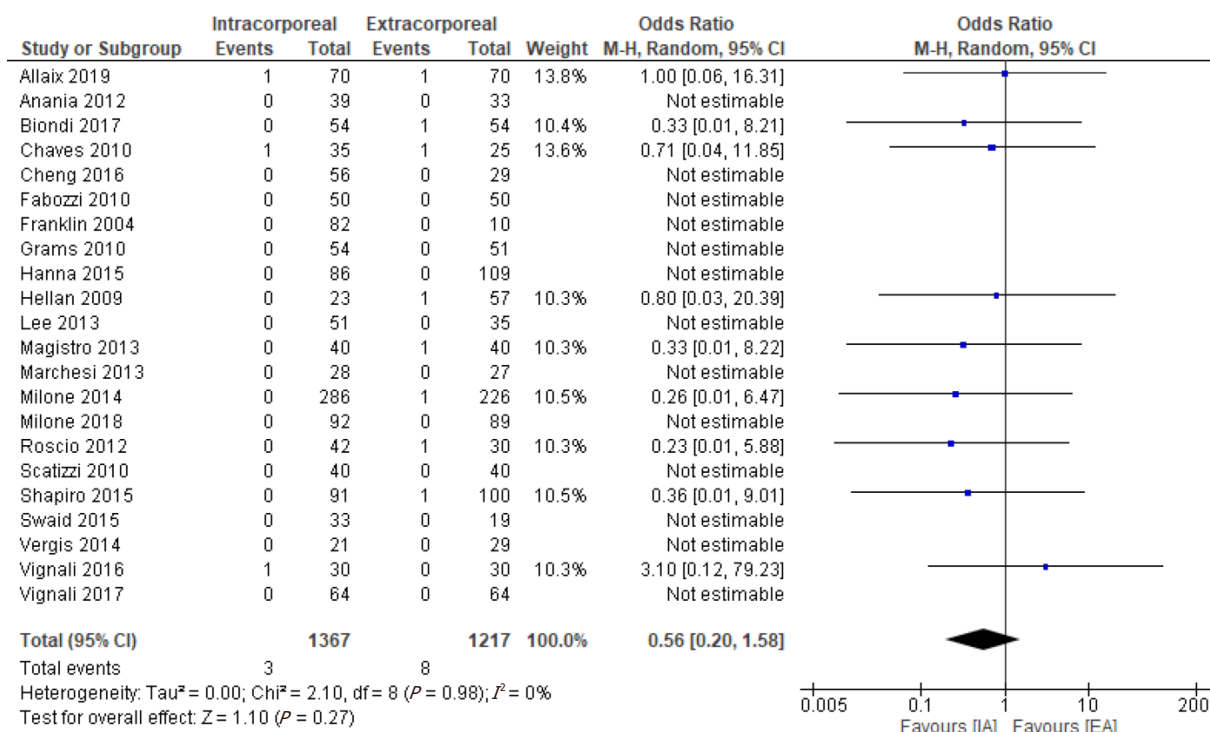


Figure 5. Meta-analysis of mortality

site infection, incisional hernia, and the need for re-intervention. On the other hand, it was considered substantial for operative time, time to first flatus, and lymph node harvesting.

Meta-regression analysis: Four covariates were assessed to determine their influences on heterogeneity, including median year of patient recruitment, retrospective vs. prospective study, study quality, and left

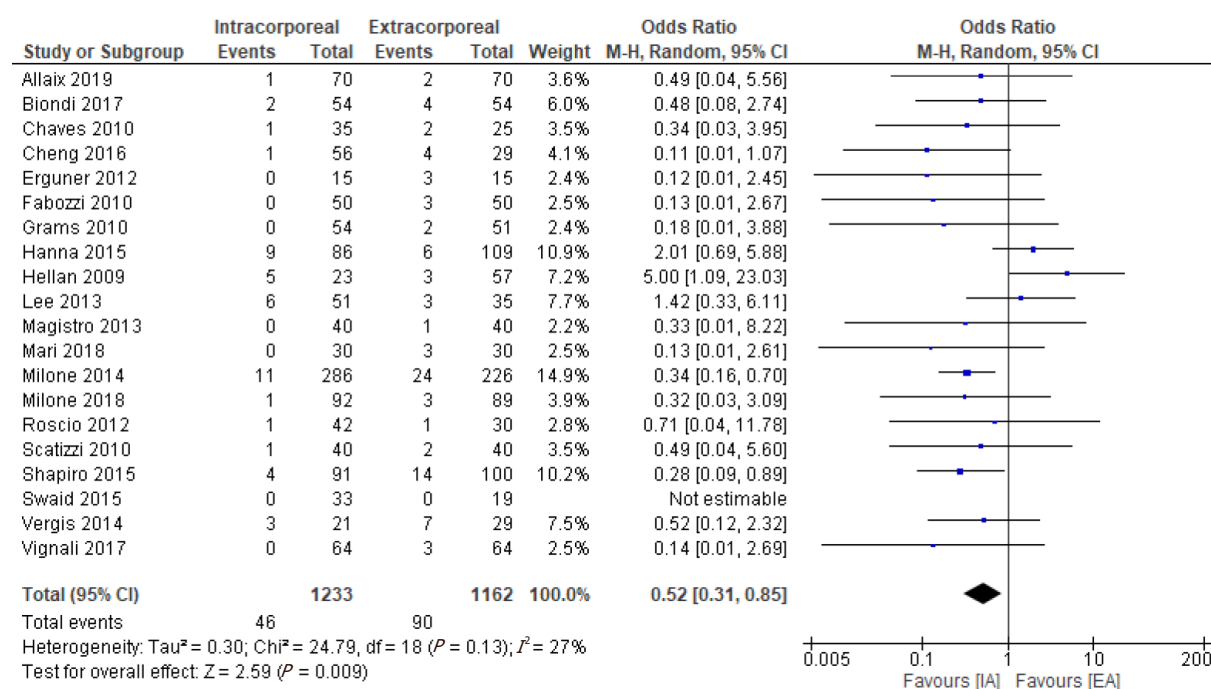


Figure 6. Meta-analysis of surgical site infection

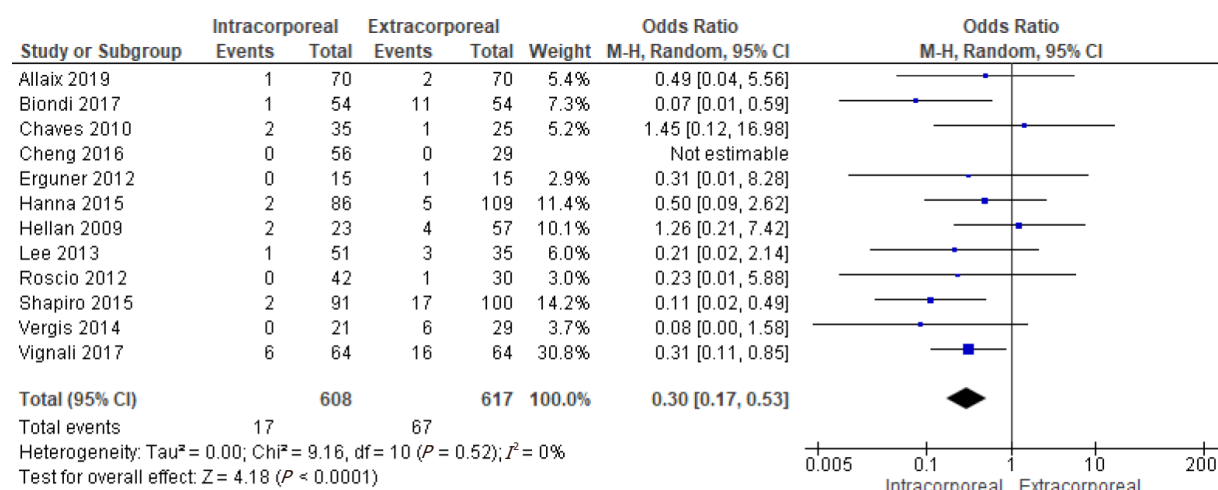


Figure 7. Meta-analysis of incisional hernia

vs. right colectomy. Univariable meta-regression did not identify any of these covariates to be a significant influence for the primary outcome.

Publication bias: No evidence of publication bias was found for the primary outcome (Begg's $P = 0.520$; Egger's $P = 0.640$). Visual examination of funnel plots for those outcomes did not demonstrate asymmetry, as evidenced in Figure 10.

Leave-one-out analysis for the primary outcome, anastomotic leakage [Figure 11], was conducted to evaluate the odds ratio when individual studies were removed. No major changes to the results were observed for anastomotic leakage (OR = 0.84; 95%CI: 0.54-1.32).

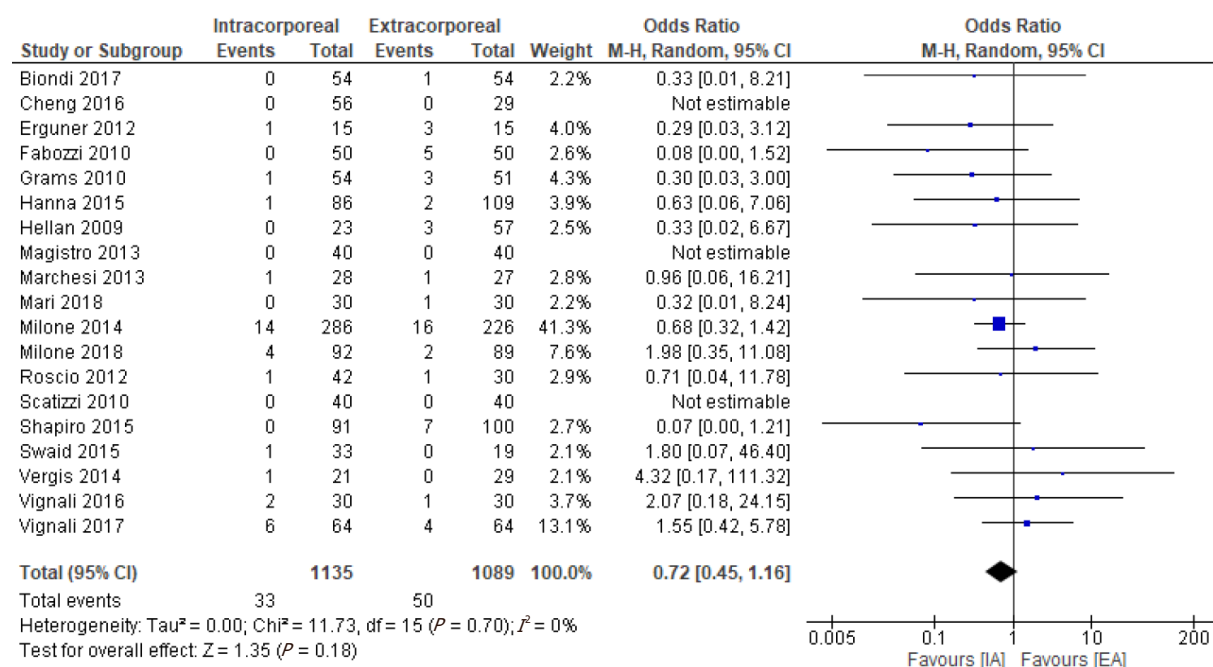


Figure 8. Meta-analysis of need for re-intervention

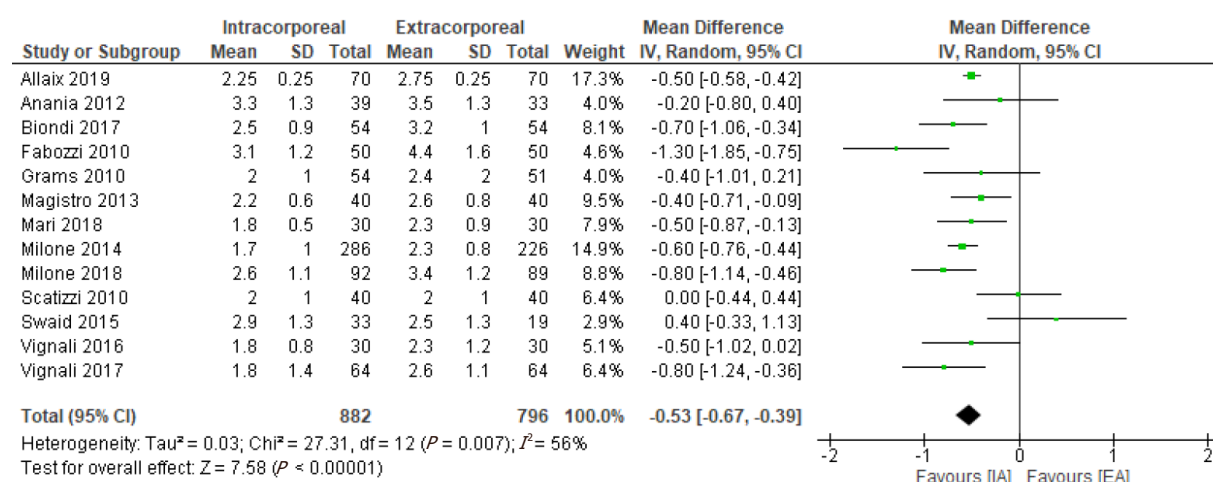


Figure 9. Meta-analysis of time to first flatus

Subgroup analysis on left colectomy

In our systematic review, only three studies were found to have met the search criteria with direct comparison on anastomotic leakage between intracorporeal and extracorporeal anastomosis in left-sided colectomy. After a careful review, only two studies^[29,33] were eligible for further analysis, with a total number of 233 patients (125 IA vs. 108 EA). A meta-analysis was conducted for the primary outcome of anastomotic leak, which did not demonstrate a significant difference between the two cohorts (OR = 1.90; 95%CI: 0.27-13.21; $P = 0.52$; $I^2 = 0\%$) [Figure 12]. However, these studies were non-randomised with a lack of long-term follow-up, and it was perceived that further subgroup meta-analysis on left colectomy alone, with Milone *et al.*^[29] imposing significantly higher weight (64.4%), would be unlikely to produce meaningful results and therefore was not conducted.

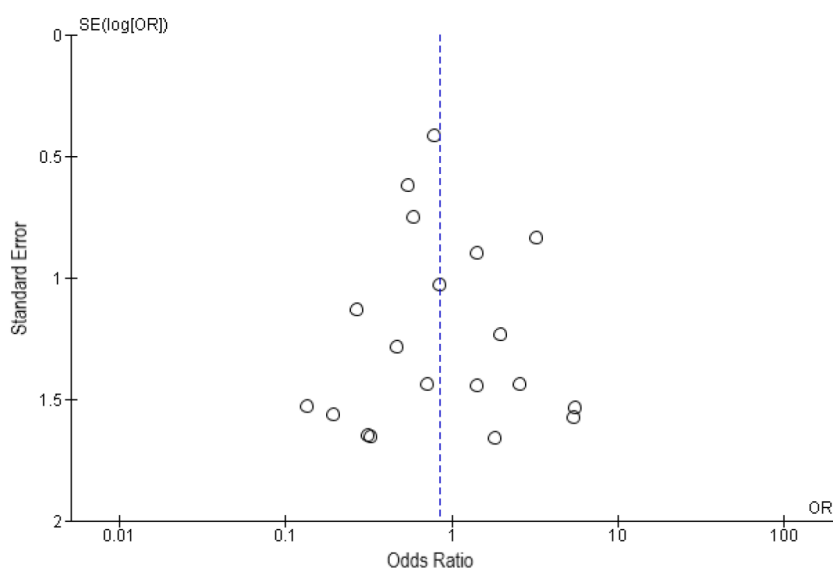


Figure 10. Funnel plot for anastomotic leak

Study	Odds Ratio [95% CI]
Omitting Allaix 2019	OR 0.76 [0.48, 1.20]
Omitting Anania 2012	OR 0.84 [0.54, 1.32]
Omitting Biondi 2017	OR 0.87 [0.56, 1.35]
Omitting Chaves 2010	OR 0.81 [0.52, 1.26]
Omitting Cheng 2016	OR 0.84 [0.54, 1.31]
Omitting Erguner 2012	OR 0.86 [0.55, 1.34]
Omitting Fabozzi 2010	OR 0.88 [0.56, 1.37]
Omitting Franklin 2004	OR 0.84 [0.54, 1.31]
Omitting Grams 2010	OR 0.86 [0.55, 1.34]
Omitting Hanna 2015	OR 0.90 [0.56, 1.44]
Omitting Hellan 2009	OR 0.82 [0.53, 1.28]
Omitting Lee 2013	OR 0.81 [0.52, 1.28]
Omitting Magistro 2013	OR 0.84 [0.54, 1.31]
Omitting Marchesi 2013	OR 0.84 [0.54, 1.31]
Omitting Mari 2018	OR 0.86 [0.55, 1.33]
Omitting Milone 2014	OR 0.87 [0.52, 1.46]
Omitting Milone 2018	OR 0.82 [0.52, 1.28]
Omitting Roscio 2012	OR 0.85 [0.54, 1.32]
Omitting Scatizzi 2010	OR 0.84 [0.54, 1.31]
Omitting Shapiro 2015	OR 0.88 [0.56, 1.38]
Omitting Swaid 2015	OR 0.83 [0.53, 1.29]
Omitting Vergis 2014	OR 0.83 [0.53, 1.30]
Omitting Vignali 2016	OR 0.81 [0.52, 1.26]
Omitting Vignali 2017	OR 0.87 [0.55, 1.38]
=====	
Random Effect Model	OR 0.84 [0.54, 1.32]

Figure 11. Leave one out analysis for anastomotic leak

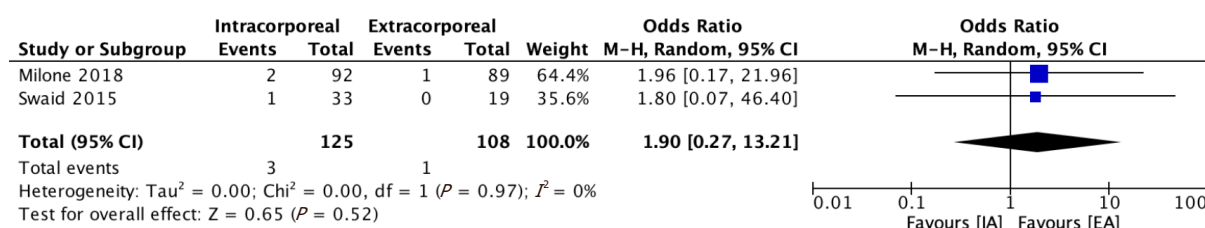


Figure 12. Subgroup meta-analysis of anastomotic leak in left colectomy

DISCUSSION

There is a growing body of evidence in the literature that intracorporeal anastomosis is a safe alternative to extracorporeal anastomosis in laparoscopic right hemicolectomy^[3-5]. However, we found that currently published systematic reviews and meta-analyses have not included more recently published studies, and have only compared right sided colectomies, with little research into left colectomies. As a result, we have carried out a new meta-analysis in an attempt to evaluate the clinical and oncological appropriateness of intracorporeal anastomosis technique, combining data on right-sided and left-sided laparoscopic colectomies and including more recently published studies. The strengths of this meta-analysis are that it provides more power to the analysis, allows for identification of more patients in each study arm through meticulous methodology, and offers thorough selection process and critical analysis of the results. To the best of our knowledge, this is the first systematic review with meta-analysis of the literature evaluating comprehensive peri-operative outcomes between IA and EA in a combined fashion including both laparoscopic right and left colectomies. Twenty-four studies were included for analysis, with an overall sample size of 2,674 patients (1,412 in the IA and 1,262 in the EA arm).

In terms of the primary outcome, the analysis supports the surgical safety of performing intracorporeal anastomosis in laparoscopic colectomy, with no statistically significant difference observed for the rate of anastomotic leakage. The quality of data is reinforced by an adequate sample size as well as an absence of heterogeneity and publication bias.

Concerning the secondary outcomes, our results from meta-analysis appear to favour IA when compared to EA, as evidenced by improved patient recovery with earlier return of bowel function, and lower rates of surgical site infections and incisional hernia, all of which were statistically significant. Moreover, this was without compromising oncological safety and short-term mortality.

Since the most common indication for laparoscopic colon resection is malignancy, it is imperative to consider the oncological safety of a surgical technique. We have selected the number of lymph nodes harvested as a surrogate marker for appropriateness of oncological radicality as the data was readily available in the literature but also an area of debate for many years. Our analysis revealed that IA was associated with slightly higher number of lymph nodes harvested. However, we acknowledge that the number of lymph nodes harvested alone does not truly represent the adequacy of oncological resection, and other crucial factors known to determine oncological safety such as clear multi-dimensional resection margins, minimal intraoperative manipulation of the tumour, and wound protection during specimen extraction all need to be considered. Therefore, we believe oncological safety would be better reflected by long-term survival and recurrence outcome. Unfortunately, only two studies, Hanna *et al.*^[36] and Lee *et al.*^[25], published meaningful long-term survival outcome with Kaplan-Meier graphs. Those studies demonstrated that there was no significant difference in both disease-free survival and overall survival at 5 years and 3 years between IA and EA cohorts respectively.

Our data demonstrated that operative time was significantly longer with the IA technique by 10 min on weighted mean difference when compared to the EA technique. Although this was statistically significant, large variations in operative time reported in included studies were reflected by serious heterogeneity in our analysis ($I^2 = 85\%$). Operative time can be influenced by a multitude of factors beyond technical aspects alone, which may include fat distribution in individual patient, adhesions from previous abdominal surgery, extension of the tumour, and/or experience of individual surgeon to account for the learning curve effect. Unfortunately, however, these potential confounders were not easily identifiable in the available studies.

The lower rates of surgical site infections and incisional hernia observed in the IA cohort may be chiefly attributed to the extraction site. The IA approach allows flexibility when choosing the location of the incision for specimen extraction. In our analysis, the most common extraction site in the IA cohort (described explicitly in 15 studies) was through Pfannenstiel incision on the suprapubic port site, which is well recognised to result in good cosmetic satisfaction with low morbidity, less pain, and lower rates of incisional hernias^[37].

The return of bowel function was faster in the IA cohort, which is consistent with the widely accepted theory that patients undergoing IA are expected to undergo reduced manipulation of the colon and mesentery. This notion is gaining considerable attention, especially in the era of growing obese population among surgical patients. A totally laparoscopic approach is thought to minimise traction injuries and risk of micro-lacerations when exteriorising the bowel through thicker abdominal walls, which is known to worsen the outcome in bowel anastomosis^[5,17]. However, the paucity in research is reflected by the fact that only one study, Vignali *et al.*^[12], 2018, was dedicated to a direct comparison between IA with EA in obese population, which did not demonstrate significant difference between the two groups in terms of peri-operative outcomes, except for the lower incidence of incisional hernia in the IA group. Further studies are thus warranted to validate this notion, which would be valuable for evidence-based safe surgical practice in an obese population.

In addition, there are two growing areas of interest for which IA could provide superior outcomes, robotic surgery and patients undergoing emergency colectomy. A 2020 meta-analysis by Genova *et al.*^[38] showed that robotic right colectomy is superior to the laparoscopic approach in terms of length of stay, time to first flatus, and overall rate of complications. Part of this difference was attributed to the rate of IA in robotic colectomy, which was 10 times higher than in laparoscopic colectomy, and when a subgroup analysis was carried out for EA in both groups, the advantages of robotic colectomy disappeared, suggesting that IA may be a strong reason for superior outcome. Di Saverio *et al.*^[39] recently published a case series of 59 emergent laparoscopic colectomies with intracorporeal anastomosis, showing that such a technique is feasible and likely safe in acute surgery. The case series demonstrated an anastomotic leak rate of 3.4% and a re-intervention rate of 3.4%, both of which are comparable to the data found by this meta-analysis. This is a novel area that warrants further research.

However, this analysis should not be taken at its face value as it is not without limitations on closer inspection. In terms of the secondary outcomes, the data collected by the studies included in this meta-analysis are overall substantially heterogeneous, making it challenging to draw robust conclusions. The lack of standardised experimental conditions is likely to have impacted on the clinical outcome measures. For example, Anania *et al.*^[15] reported that the authors did not standardise the surgical steps of extracorporeal anastomosis in right hemicolectomy, although the intracorporeal technique was uniform. Additionally, it is unclear whether some of the peri-operative measures known to improve patient outcomes were implemented. For example, it was unknown if the ERAS (enhanced-recovery-after-surgery) protocol, pre-operative bowel preparation, or prophylactic antibiotics were administered.

Therefore, we suggest that prudential interpretation around clinical significance rather than statistical significance is considered. Most available studies included in our analysis are merely observational without randomisation and are of retrospective design, the quality of which was assessed to be not very high based on IHE assessment.

In conclusion, this systematic review and meta-analysis on the comparative studies between IA and EA in laparoscopic colectomies has demonstrated IA can be safely considered by laparoscopic surgeons for resection of benign and malignant pathology in right and left colon without compromising oncological radicality. However, various limitations in the current data identified by this study need to be addressed by high-quality randomised trials involving longer follow-up.

DECLARATIONS

Authors' contributions

Study conception and design, data acquisition: Park SSW, Smith S

Data analysis and interpretation, drafting the article, critical revision of article, final approval of manuscript: Park SSW, Feng D, Smith S

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Endoscope-assisted transcranial surgery for anterior skull base meningiomas

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Abstract

Anterior skull base meningiomas are benign, dural-based tumors that originate from the tuberculum sellae, planum sphenoidale or olfactory groove. A multitude of traditional transcranial approaches have been effectively used for resection of these tumors. However, in the era of minimally invasive neurosurgery, the endoscopic endonasal and the endoscope-assisted or endoscope-controlled supraorbital keyhole eyebrow approaches stand out as the two main options utilized to resect these tumors. The supraorbital keyhole approach minimizes brain retraction, tissue dissection and length of the skin incision. Consequently, this approach is associated with a lower complication profile and much better cosmetic results in comparison to classic approaches. With endoscopic assistance or control, the approach provides an excellent view of anterior skull base meningiomas and enables optic nerve decompression when angled scopes are used. In our opinion, endoscopes will ultimately replace the surgical microscopes as the viewing tools in this type of surgery. A limited number of studies have directly compared the endoscopic endonasal approach versus the supraorbital keyhole one for resection of anterior cranial base meningiomas. In these studies, scores and algorithms have been suggested to help select the suitable approach. The practical value of these algorithms still needs to be validated by further research. Although the endoscope-assisted or -controlled supraorbital keyhole approach offers a minimally invasive and highly effective approach for excision of anterior cranial base meningiomas, the ideal approach should be tailored to the individual patient according to the tumor size, lateral extension, optic canal involvement, extent of vascular encasement and surgeon's experience.

Keywords: Endoscope, endoscope-assisted, keyhole, meningioma, olfactory groove, planum sphenoidal, skull base, tuberculum sellae



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INTRODUCTION

Anterior skull base meningiomas are benign, dural-based tumors that originate from the tuberculum sellae, planum sphenoidale or olfactory groove which includes the lamina cribrosa and frontoethmoidal suture. Olfactory groove meningiomas account for 8%-13% of all intracranial meningiomas^[1-3], while tuberculum sellae and planum sphenoidale meningiomas constitute around 10%-15% of meningiomas and often present with visual disturbance due to compression of the optic nerves and chiasm^[4,5] [Figure 1].

From a pathoanatomical point of view, tuberculum sellae meningiomas are in close anatomical proximity to the optic nerves, optic chiasm, internal carotid artery, and anterior cerebral artery, as well as the hypothalamus, infundibulum and pituitary gland [Figure 2]. In comparison to planum sphenoidale meningiomas, true tuberculum sellae meningiomas are centered on the tuberculum sellae and grow posterosuperiorly displacing the optic nerves superolaterally^[6] [Figure 3]. Furthermore, tumor extension into one or both optic canals as well as vascular encasement can take place in many cases and adds to the technical difficulty of resecting these tumors [Figure 4]. On the other hand, olfactory groove meningiomas are in close apposition to the olfactory nerves and tend to infiltrate the cribriform plate, invade the ethmoid and sphenoid sinuses, and engulf the anterior clinoid process as well as the vasculature in their vicinity^[1,3,7,8].

Surgical excision is the main treatment modality for these tumors and should ideally aim at complete removal of the tumor as well as the dural tail and invaded bone^[9], obviously not an easily achievable or even impossible task when it comes to meningiomas of the skull base, owing to the nature of the anatomical environment surrounding these tumors. Subtotal resection followed by radiation therapy may therefore be an acceptable option in some cases^[10]. Especially for tuberculum sellae and planum sphenoidale meningiomas, surgical resection results in decompression of the optic nerves and chiasm and therefore prevents further visual deterioration and may reverse neural damage in some cases^[10].

Currently, minimally invasive approaches for surgical excision of anterior skull base meningiomas include the endoscopic endonasal approach^[11-14] and the endoscope-assisted or endoscope-controlled supraorbital keyhole eyebrow approach^[7,15-19]. In this article, the endoscope-assisted or endoscope-controlled supraorbital keyhole eyebrow approaches for anterior cranial base meningiomas will be briefly elaborated upon.

SHIFT TOWARDS MINIMALLY INVASIVE APPROACHES FOR ANTERIOR SKULL BASE MENINGIOMAS

Over several decades, a multitude of traditional transcranial approaches have been developed and effectively used for resection of anterior skull base meningiomas. These approaches include the pterional, bifrontal, extended bifrontal, transbasal, orbitozygomatic, and interhemispheric approaches^[2,20-26]. Notwithstanding, morbidities related to brain retraction, superior sagittal sinus transection, frontal sinus transgression, optic nerve or chiasm manipulation and wound healing problems^[27,28] led to a quest for less invasive alternatives.

Paving the way for the evolution of minimally invasive neurosurgery, advances in the fields of surgical technology, microsurgery, neuroradiology and neuroendoscopy have orchestrated the development of an array of innovative and less traumatizing solutions geared at treating a large spectrum of brain and skull base disorders. Along with this rising tide, novel surgical approaches were developed to treat various pathologies of the anterior skull base including meningiomas originating therein. Probably having more impact than others, advances in endoscopic technology have significantly contributed to the development and refinement of these approaches as they are practiced nowadays. Undeniably, minimally invasive

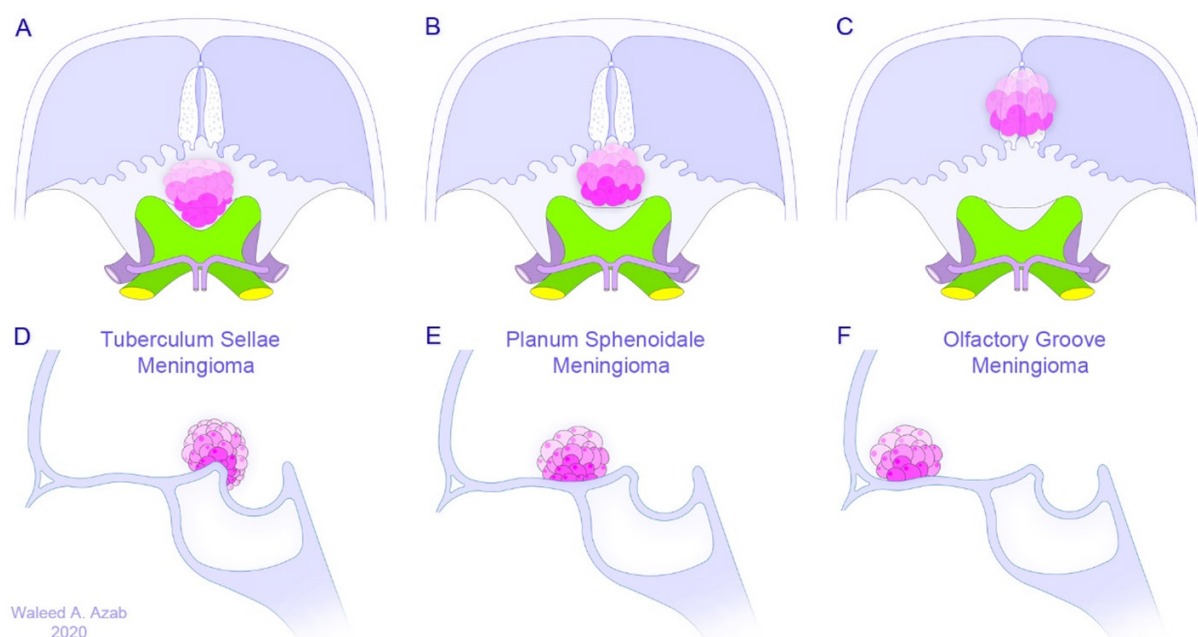


Figure 1. Nomenclature of anterior skull base meningiomas according to anatomical origin in axial (A-C) and sagittal (D-F) views

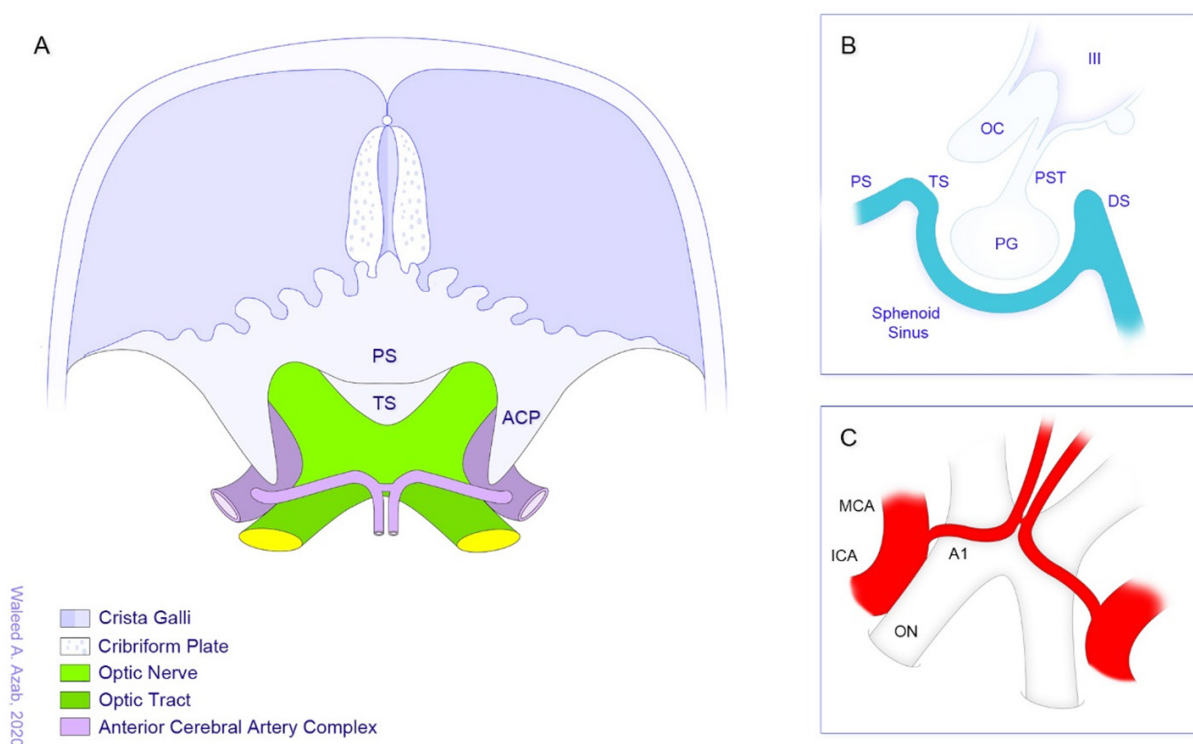


Figure 2. Anatomical environment and structures often related to anterior skull base meningioma. A: axial overview; B: sagittal view of the sellar region and structures in its vicinity that may be involved especially in tuberculum sellae and planum sphenoidale meningiomas; C: view of the optic apparatus and the neighboring vasculature. A1: first segment of anterior cerebral artery; ACP: anterior clinoid process; DS: dorsum sellae; ICA: internal carotid artery; MCA: middle cerebral artery; OC: optic chiasm; ON: optic nerve; PG: pituitary gland; PS: planum sphenoidale; PST: pituitary stalk; TS: tuberculum sellae; III: third ventricle

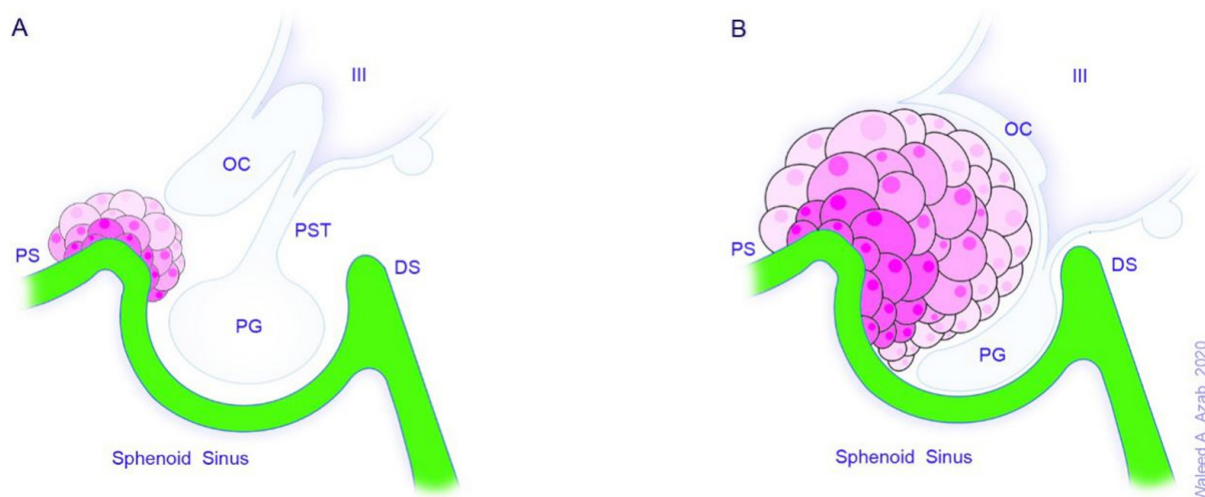


Figure 3. Tuberculum sellae meningiomas can be small (A) or large (B) and are centered on the tuberculum sellae. They grow posterosuperiorly displacing the optic nerves superolaterally. Note the intrasellar extension and compression of the neighboring structures. DS: dorsum sellae; OC: optic chiasm; PG: pituitary gland; PS: planum sphenoidale; PST: pituitary stalk; TS: tuberculum sellae; III: third ventricle

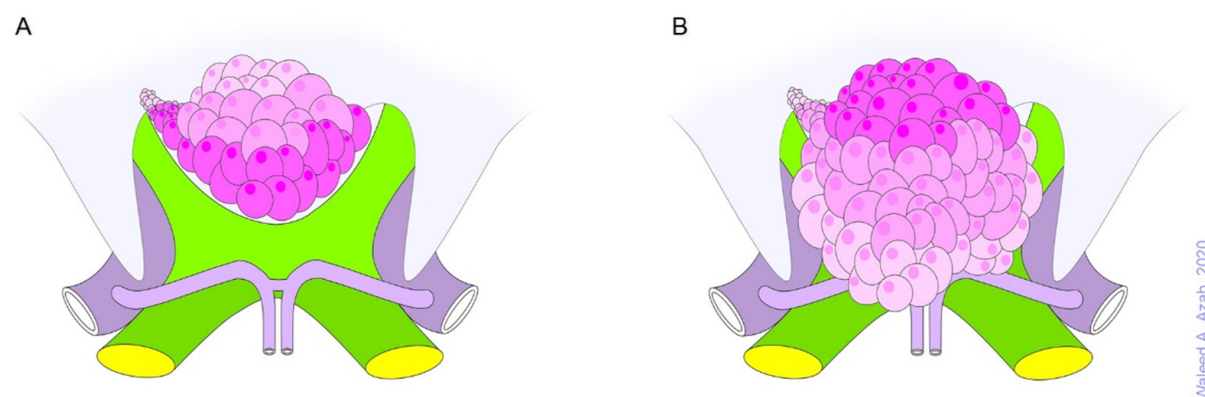


Figure 4. Tuberculum sellae meningiomas frequently extend into the optic canal (A) and may also encase blood vessels in the vicinity (B)

approaches have been shown to be associated with less operative risks, comparable or even better outcomes, more satisfying cosmetic results and faster recovery times in comparison to the classic transcranial approaches^[19,27,29].

ENDOSCOPE-ASSISTED AND ENDOSCOPE-CONTROLLED SUPRAORBITAL KEYHOLE APPROACHES

In 1908, Fedor Krause was the first to describe a supraorbital subfrontal exposure to excise an anterior skull base meningioma^[30]. Later on, Charles Frazier in 1913 used a supraorbital craniotomy with removal of the orbital rim and roof for surgical resection of a “pituitary cyst” that he described as “seen projecting upward between optic tracts”. In Frazier’s description, the procedure offered “a splendid exposure of the region of the sella turcica”^[31]. Donald Wilson was the first to use the term “Keyhole Surgery” in his description of a variety of approaches for supratentorial pathologies. He used small linear incisions and a 2- inch D’Errico trephine to create limited craniotomies that were however sufficiently large to operate through. In his technical note “Limited Exposure in Cerebral Surgery”, published in 1971, he pointed out that such operating methodology avoided unnecessary exposure of brain tissue and thus its potential

damage, and was also associated with better cosmetic results^[32]. Many decades after these pioneering works, Axel Perneczky popularized the supraorbital keyhole approach through an eyebrow incision and solidly demonstrated the importance of endoscopic assistance in this approach through many published large series of vascular and tumor cases^[18,19,29,33].

Compared to classic transcranial approaches, the supraorbital keyhole approach minimizes brain retraction, tissue dissection and length of the skin incision. Temporalis muscle dissection is also very limited so that temporalis muscle atrophy and the consequent mandibular pain and chewing problems are almost nonexistent. Needless to say, the approach yields much better cosmetic results than classic approaches^[18,33,34]. Much more than what is expected from a mini-craniotomy, the supraorbital eyebrow exposure offers a larger field of view with increasing the distance from the craniotomy as is the case with any keyhole approach^[29,34,35]. Especially with endoscopic assistance or control, the approach truly provides an excellent view of anterior skull base meningiomas. Additionally, optic nerve decompression is possible under endoscopic view when angled scopes are used^[36]. Recently, the pure endoscopic (endoscope-controlled) supraorbital keyhole approach has been used in place of the endoscope-assisted method with promising results^[36,37].

ROLE OF THE RIGID ENDOSCOPE IN THE SUPRAORBITAL KEYHOLE EYEBROW APPROACH

The idea of endoscopic assistance in cranial surgery emerged out of the need to operate via a small opening and yet obtain an appropriate visualization and control of the structures within the field, that is, to perform a minimally invasive yet maximally effective surgery. A closer look at the early beginnings of adopting this surgical philosophy sheds the light on how rigid endoscopes were capable of fulfilling this goal by surmounting the hurdle of suboptimal visualization when a small exposure is used.

In 1974, Werner Prott - an otosurgeon from the University of Würzburg- used a rigid endoscope to explore and operate within the cerebellopontine angle. At that time, he preferred a transpyramidal retrolabyrinthine approach via Trautmann's triangle. A bone flap of 1 cm diameter was made after performing a mastoidectomy and the endoscope was inserted through this narrow space confined between the sigmoid sinus, the superior petrosal sinus, the posterior semicircular canal and the endolymphatic sac without damaging any functional structure of the inner ear or of the cerebellum^[38]. The same approach was used by Falk Oppel in 1981 for sectioning the sensory root of the trigeminal nerve, glossopharyngeal nerve, and cranial part of the vagus to treat an intractable facial pain in one patient with recurrent deeply seated carcinoma of the upper jaw. The patient's general condition did not permit surgical exploration of the posterior fossa and a "minor" procedure was therefore necessary^[39].

Indeed, one of the greatest advantages of a rigid endoscope is that it brings light inside the surgical field, a feature that results in a very highly illuminated area of interest. Moreover, the close proximity of the light source to the structures being viewed eliminates shadows within the field, adding to the extreme clarity of the viewed images. Such superiority of the endoscopic view is also brought about by the high color fidelity and image definition capabilities of today's state-of-the-art rigid endoscopes. Notably, one of the very important optical properties of the rigid endoscope is the greater depth of focus, which simply means that the viewed objects remain in focus within a greater range of distances from the viewing lens. This means lesser need to adjust the focus of the endoscope during the procedure, a feature that results in a seamless operative workflow. The use of angled scopes also enables "looking around the corners", and thereby adds further to the efficacy and safety of the procedure as it brings concealed tumor remnants into view and obviates the need for retraction of neurovascular structures.

On the contrary, the microscope in keyhole surgery requires frequent changing of the viewing angle to allow illumination and visualization of the area of interest deep in the surgical field^[40], an inevitable

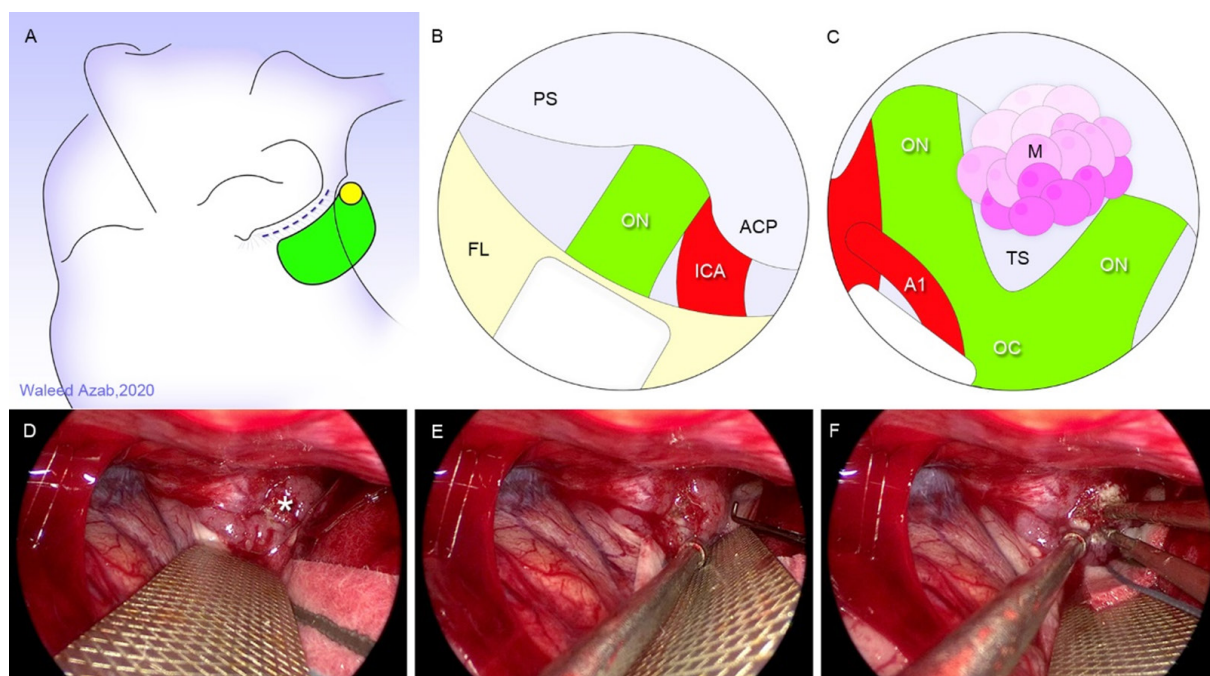


Figure 5. Endoscope-controlled supraorbital keyhole eyebrow approach. A: head position, skin incision, burr hole placement and craniotomy design; B: initial endoscopic view gained through right-sided approach; C: further brain relaxation and panoramic exposure of a tuberculum sellae meningioma; D-F: intraoperative endoscopic views of tuberculum sellae meningioma (asterisk) being exposed with plane development and bipolar coagulation, left-sided approach. A1: first segment of anterior cerebral artery; ACP: anterior clinoid process; ICA: internal carotid artery; FL: frontal lobe; OC: optic chiasm; ON: optic nerve; PS: planum sphenoidale; TS: tuberculum sellae (Illustrations A through C by Waleed Azab)

consequence of the light source and the viewing lens being located outside the craniotomy. The loss of light energy at the edges of the small craniotomy and the dropped shadows on the structures within the field further contribute to the lesser quality of the microscopic view obtained during supraorbital keyhole surgery.

Notwithstanding, some disadvantages of endoscope-assisted surgery exist and include the lack of three-dimensionality, need for familiarity with endoscopic devices, need to develop eye-hand coordination, and imitation of the operating range of instruments^[34]. Such disadvantages, however, are largely outweighed by the higher visual quality, surgical radicality and lesser complication profile offered by this type of surgery. In our opinion, rigid endoscopes are indispensable components of the array of surgical tools required to perform a keyhole supraorbital approach. We truly believe endoscopes will completely replace surgical microscopes for this type of surgery in the future.

SURGICAL TECHNIQUE OF THE SUPRAORBITAL KEYHOLE EYEBROW APPROACH [FIGURE 5]

The surgical technique of the supraorbital keyhole eyebrow approach has been extensively described in the literature^[19,29,35,41-46]. A brief description of the technique will be given below.

Preoperative planning

Careful case selection is paramount when operating via the supraorbital eyebrow approach. The patient's individual anatomy should be thoroughly evaluated. One important consideration is the lateral extent of the frontal air sinus which dictates the medial border of the supraorbital craniotomy and determines whether an appropriate surgical trajectory would be possible. Meningiomas with high superior extent need more retroflexion of the head to obtain a proper working trajectory. In general, the closer the tumor to the

posterior wall of the frontal bone, the more contralateral head rotation is required. Neuronavigation is very important for planning the procedure and should be used in all cases.

Under general anesthesia with the patient in the supine position, the head is secured in a MAYFIELD skull clamp® and rotated 25°-30° to the left for a right-sided approach. The head is then extended 10°-15° to allow a gravitational fall of the frontal lobe away from the skull base. This helps decreasing the brain retraction required to develop the operative corridor. Slight contralateral lateral flexion is then undertaken to help provide easier instrument maneuverability during the procedure.

Skin incision

The skin incision lies within the eyebrow and starts just lateral to the supraorbital notch - to avoid injury to the supraorbital nerve and consequent postoperative forehead numbness- and ends at the lateral end of the eyebrow over the zygomatic process. In some cases, the incision may be extended laterally a further 5-10 mm in a skin crease without significant cosmetic sequelae.

At the superior temporal line, the temporalis fascia is incised using the monopolar coagulation for about 2 cm and the frontalis fascia is then cut from the temporal line in a semicircular fashion over the frontal bone with its base at the orbital rim. The temporalis muscle is subsequently dissected off the bone and retracted posteriorly for 1-2 cm.

Craniotomy

A single burr hole is made using a sharp pit attached to the high-speed drill in the temporal fossa lateral to the superior temporal line. The burr hole position is chosen at a point that is slightly higher than the classic MacCarty's burr hole. A frontal direction of drilling prevents entering the orbit. A craniotome is then used to perform a 2-3.5 cm × 2-2.5 cm bone flap. Care should be taken to avoid opening the frontal air sinus at the medial border of the craniotomy. Small bony extensions of the frontal skull base should be drilled off extradurally and the inner edge of the craniotomy is to be beveled to increase the space available for instrument maneuverability and to gain unobstructed view in the depth of the field.

Dural opening and intradural steps

The dural flap is fashioned with its base at the orbital roof. Under microscopic or endoscopic control, the subfrontal corridor is developed. The ipsilateral optic nerve and supraclinoid carotid artery are identified, and the arachnoid membranes of the optico-carotid and carotid-oculomotor cisterns are opened to allow CSF egress. CSF release is essential to achieve adequate brain relaxation that opens the surgical corridor. The rigid 4-mm endoscope is held by an assistant or fixed by a holder during an endoscope-controlled procedure. An irrigation sheath is very helpful to clear the smudged lens. Surgery then proceeds using the standard microsurgical techniques. It should be noted that tuberculum sellae meningiomas grow in a subchiasmatic location displacing the optic chiasm backwards and the optic nerves laterally and superiorly creating a prechiasmatic working space and facilitating the resection of these tumors via a supraorbital eyebrow approach^[47]. In far anterior olfactory groove meningiomas, visualization of the attachment point of the tumor in the midline depression of the olfactory groove may not be possible with the operating microscope. This can be overcome with an angled endoscope and angled instruments^[35]. Wound closure is then undertaken in the usual manner.

Approach selection for anterior skull base meningiomas: endoscope-assisted supraorbital keyhole versus endoscopic endonasal surgery

Advances in endoscopic technology^[48] and the subsequent development of the expanded endoscopic endonasal approach^[6,49] created significant controversy regarding whether an endonasal or a keyhole supraorbital approach provides the best results^[6,10,50]. On the one hand, the advantages of endoscopic

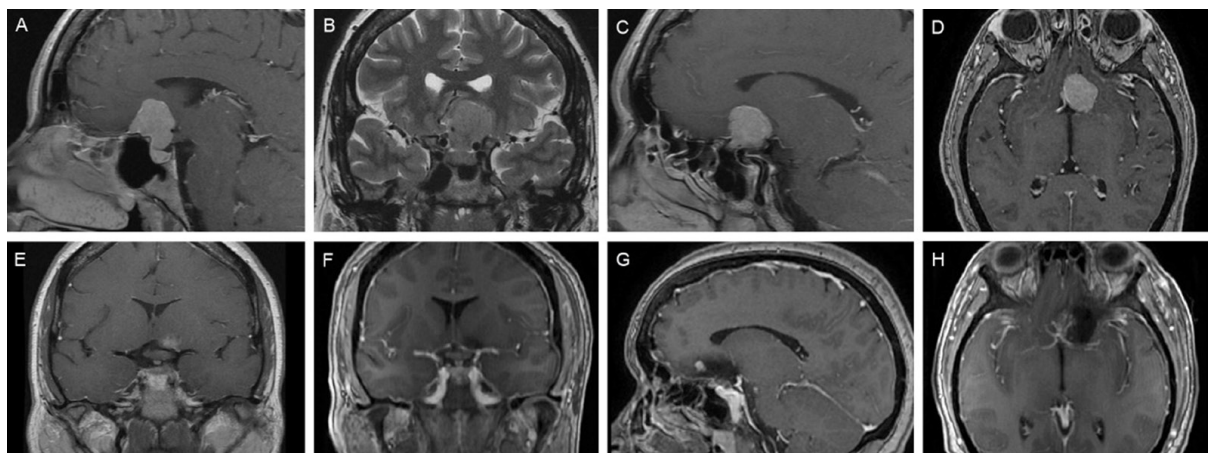


Figure 6. Pre- (A-E) and postoperative (F-H) magnetic resonance images in a case of tuberculum sellae meningioma excised via an endoscope-controlled keyhole supraorbital approach. Extension beyond the internal carotid on the left and anterior cerebral artery encasement on the right led to selection of endoscope-assisted keyhole transcranial approach instead of an extended endoscopic endonasal transsphenoidal approach

endonasal over supraorbital keyhole approach include early devascularization of the tumor, less manipulation of the optic nerves, chiasm and brain, better visualization of the medial optic canal allowing removal of intracanalicular tumor extensions, removal of all involved bone at the skull base and access to potentially invaded intranasal structures such as the ethmoid cells^[10,34,51]. The advantages of the supraorbital keyhole over the endoscopic endonasal approach, on the other hand, include avoidance of an infected field, avoidance of trauma to the nasal passages and olfactory mucosa, and a wider view of the lateral extent of the tumor, making it more suitable for tumors with extension lateral to the carotid artery or optic nerve and for tumors with vascular encasement^[10,34]. Although CSF leaks are less frequent following the supraorbital keyhole approach, the incidence of CSF leakage that initially complicated expanded endonasal skull base approaches has been reduced dramatically with the advent of the nasoseptal flap^[6,52].

Across the literature, a limited number of studies exist that directly compare the endoscopic endonasal versus supraorbital keyhole approach for resection of anterior cranial base meningiomas. In these studies, scores and algorithms have been suggested to help select the suitable approach^[3,6,27,42,50,53] [Figure 6]. As a matter of fact, one of the important factors that lessen the credibility and practical applicability of the results of such studies, however, is that the indications for each approach may differ, and it is impossible to compare two approaches for removal of the very same tumor^[10].

Although a detailed account of the published results is beyond the scope of this review, it is important to note that for olfactory groove meningiomas, the endoscope-assisted supraorbital eyebrow approach leads to a higher extent of resection and lower rate of complications than the purely endoscopic endonasal approach^[7]. while for tuberculum sellae and planum sphenoidale meningiomas, the two approaches yield more or less similar rates of gross total resection, near total resection and visual recovery^[34]. It should be borne in mind that not all anterior skull base meningiomas are amenable to minimally invasive approaches^[27].

In a recently published meta-analysis, Khan *et al.*^[54] compared the endoscope-assisted supraorbital keyhole approach with the microscopic transcranial and expanded endoscopic endonasal approaches for surgical resection of olfactory groove and tuberculum sellae meningiomas. In the authors conclusions, case selection was paramount in establishing the role of endoscope-assisted keyhole surgery in these tumors.

In our opinion, the ideal approach should be tailored to the individual patient according to the tumor size, lateral extension, optic canal involvement, extent of vascular encasement and surgeon's experience. We currently make the selection of the approach on a case-by-case basis without following a specific algorithm.

CONCLUSION

Endoscope-assisted or endoscope-controlled supraorbital keyhole transcranial approach is a highly effective approach for excision of anterior skull base meningiomas. It offers a minimally invasive option that overcomes the pathoanatomical constraints that preclude using an extended endoscopic endonasal approach in some cases.

DECLARATIONS

Authors' contributions

All authors made substantial contributions to the conception and design of the article, performed data acquisition, and provided administrative, technical and material support as well: Azab WA, Elmaghraby MA, Zaidan SN, Mostafa KH

Made the illustrations for the article: Azab WA

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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The endoscope and instruments for minimally invasive neurosurgery

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Abstract

The advent of neuroendoscopy catalyzed the ongoing development of minimally invasive neurosurgery in the 1990s. This millennium has seen rapid developments in the design of scopes, improved high-definition visualization systems, and a plethora of dedicated instruments. Many minimally invasive and endoscopic procedures have become the new “standard of care” today. Endoscopic third ventriculostomy and endonasal pituitary surgeries have replaced alternative techniques in most major institutes in the world and the indications are rapidly increasing to tackle many midline skullbase, intraventricular, and some parenchymal lesions as well. The scope of minimally invasive neurosurgery has extended to spine surgery, peripheral nerve surgery, and unique indications, viz. craniosynostosis repair. This review describes many of these developments over the years, evaluates current scenario, and tries to give a glimpse of the “not so distant” future.

Keywords: Hydrocephalus, endonasal endoscopic approach, minimally invasive neurosurgery, minimally invasive spine surgery, neuroendoscopy, skullbase, ventricular surgery

INTRODUCTION

Minimally invasive surgery has become the “standard of care” over the last 50 years in various branches of surgery. Although endoscopic neurosurgery for hydrocephalus took roots quite early, it took much longer for the other procedures to develop until the introduction of dedicated scopes and appropriate instrumentation. Endoscopic third ventriculostomy became a real alternative to shunt surgery for



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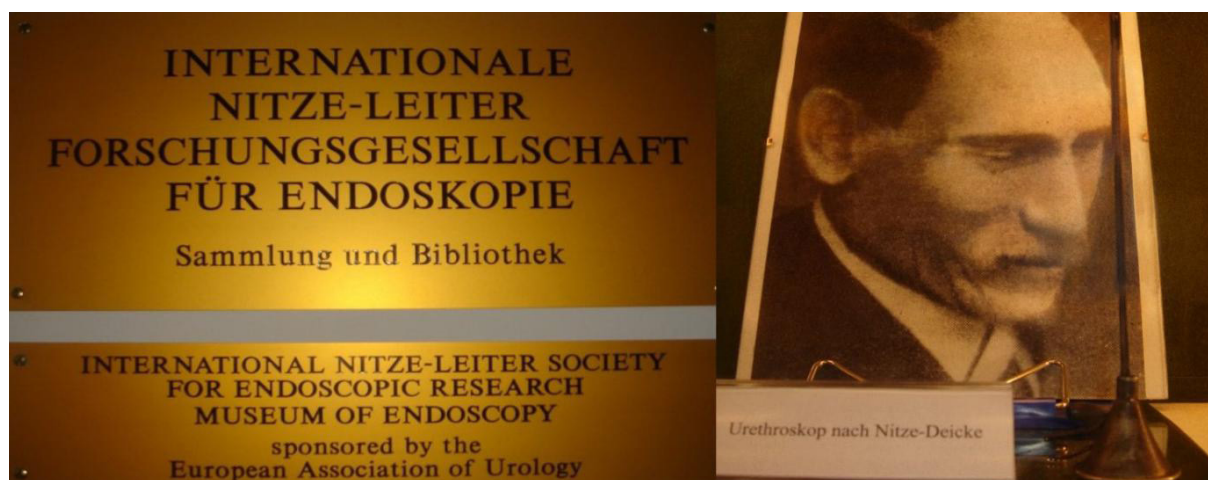


Figure 1. Maximilian Nitze's urethroscope kept on display at the endoscopy museum at Vienna

hydrocephalus only 25 years ago. Its widespread application to intraventricular procedures was the next logical progression. Simultaneously, the popularity of functional endoscopic sinus surgery logically extended to neurosurgery of the skullbase. Tubular retractor systems developed for minimally invasive spinal neurosurgery were then well supported by endoscopy. Endoscopy for minimally invasive neurosurgery can be broadly considered to be of three types^[1]: (1) purely endoscopic surgery (channel endoscopy); (2) endoscope guided surgery (endonasal or port surgery); and (3) endoscope assisted microsurgery.

The commonly performed “purely endoscopic procedures” include third ventriculostomy, septostomy, aqueductoplasty, and biopsies. The “endoscopic guided procedures” can be performed purely by endoscopy as well but may require assistance by instruments outside the scope, such as for most endonasal pituitary, skullbase procedures and intraventricular tumors. The “endoscopy assisted procedure” could be any standard microsurgical procedure wherein endoscopy provides special benefits of looking around the corners as in the case of vestibular schwannomas, epidermoid, and various other skullbase surgeries. It also helps in aiding and confirming hemostasis in areas which cannot be easily approached without too much brain retraction. The endoscope and its related accessories/instruments remain the backbone of any of these endoscope-dependent techniques^[2,3].

The present paper traces the evolution of endoscopic techniques as applied to neurosurgery and describes the available armamentarium for the aid of neurosurgeons.

DISCUSSION

Evolution of neuroendoscopy

The basic principle of endoscopy lies in the illumination and internal reflection of light in a body cavity. This principle has been worked upon by many scientists even before the era of modern medicine. Greek scientist Hippocrates' work published in the book “The Art of Medicine” and Arab-Spanish surgeon Abul-Qasim's techniques from the book “Al-Tasrif” (The Method) are testament to the fact that endoscopy had its origins many years earlier than previously thought^[4]. For his description and application of the first prototype of an endoscope, German physician Philip Bozzini is widely, albeit contentiously, regarded as the “Father of Endoscopy”^[5]. The first therapeutic application of endoscopy was in the field of urology in 1873 by Joseph Grunfeld from Austria. This was closely followed by the development of the first direct-vision rigid endoscopes (cystoscope) in 1877 by Maximilian Nitze^[6] [Figure 1]. The inbuilt light source system effectively corrected the persistent issues with illumination in the application of endoscopy.

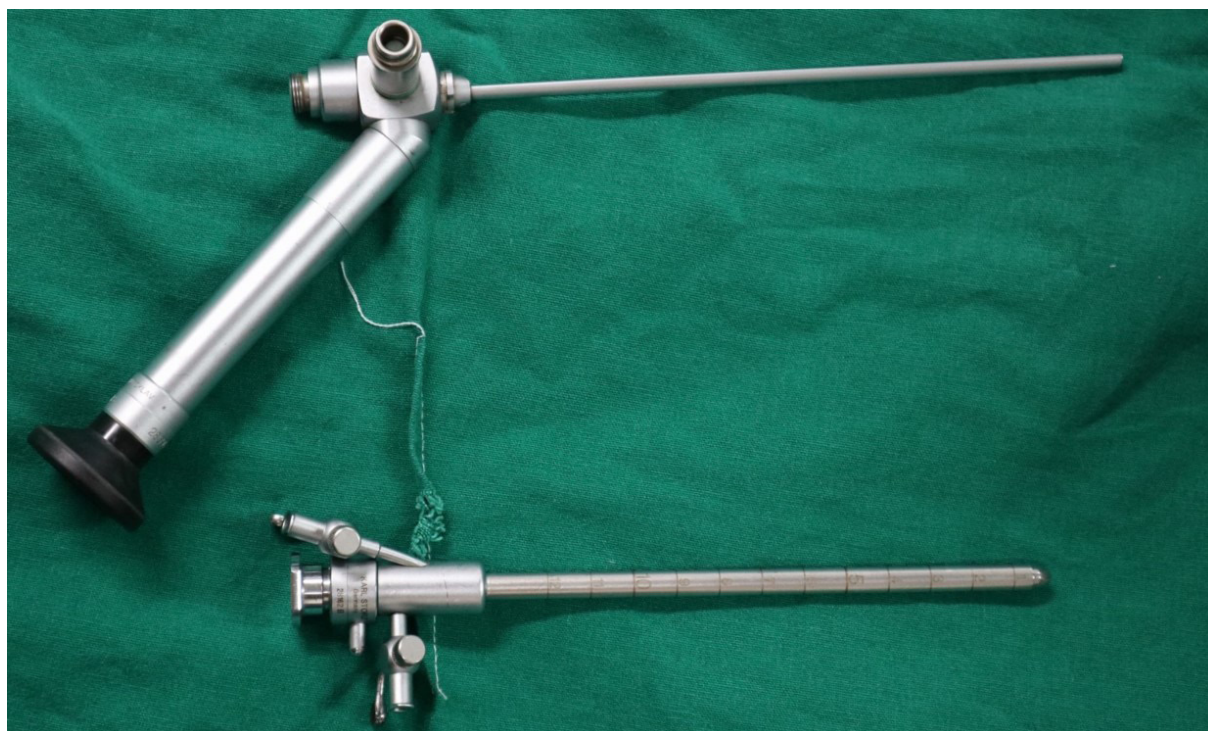


Figure 2. Gaab scope with obturator. The side channel allows ultrasonic surgical aspirator shaft to pass through

The scope system then underwent several technical modifications before being implemented widely in the field of surgery. Victor Lespinasse, Walter Dandy, and William Mixter were the pioneers for introducing endoscopy in neurosurgery. The earliest instruments used for this purpose were cystoscopes and urethoscopes. Use in neurosurgery was therefore limited due to the rigid nature of the instrument, suboptimal optics, and large size of the scopes. Although the term ventriculoscopy was first used by Walter Dandy in 1922 while describing his unsatisfactory experience with a cystoscope, the first ventriculoscope was described a few years later by Tracy Putnam and thereafter perfected by John Scarff^[7].

The major improvement in optical imaging was brought about by renowned British Physicist, Professor Harold Hopkins. He was the foremost authority in his field and is credited for introducing concepts of zoom lens, rod-lens endoscopes, and rigid/flexible endoscopes. The rights to his work on the lens system for endoscope were purchased by Karl Storz SE & Co. KG from Germany in the 1960s, and, until now, surgeons from the world over are taking benefit of this partnership^[8].

Takanori Fukushima from Japan used a fiberscope in 1973 for intraventricular as well as subarachnoid space endoscopic surgery with malleable instruments but the poor picture quality in the fiberscope made it unpopular^[9]. The introduction of side viewing wide angled lens by Michael Apuzzo ushered in the era of modern neuroendoscopy, an era which would be subsequently based upon a foundation of clarity, illumination, maneuverability, and allowed widespread application. A channel endoscope dedicated to intraventricular neuroendoscopy was initially developed by Michael Gaab from Germany (for Karl Storz) [Figure 2]. Subsequently, additional channels were modified onto a rigid endoscope by Philippe Decq from Paris in 1996 [Figure 3], and it was clinically applied for ventriculocystocisternostomy in suprasellar arachnoid cysts and for purely endoscopic colloid cyst excision^[10,11]. This enabled simultaneous usage of unipolar or bipolar probe biopsy forceps along with suction and irrigation and helped expand the armory of neuroendoscopy by allowing bimanual dissection.

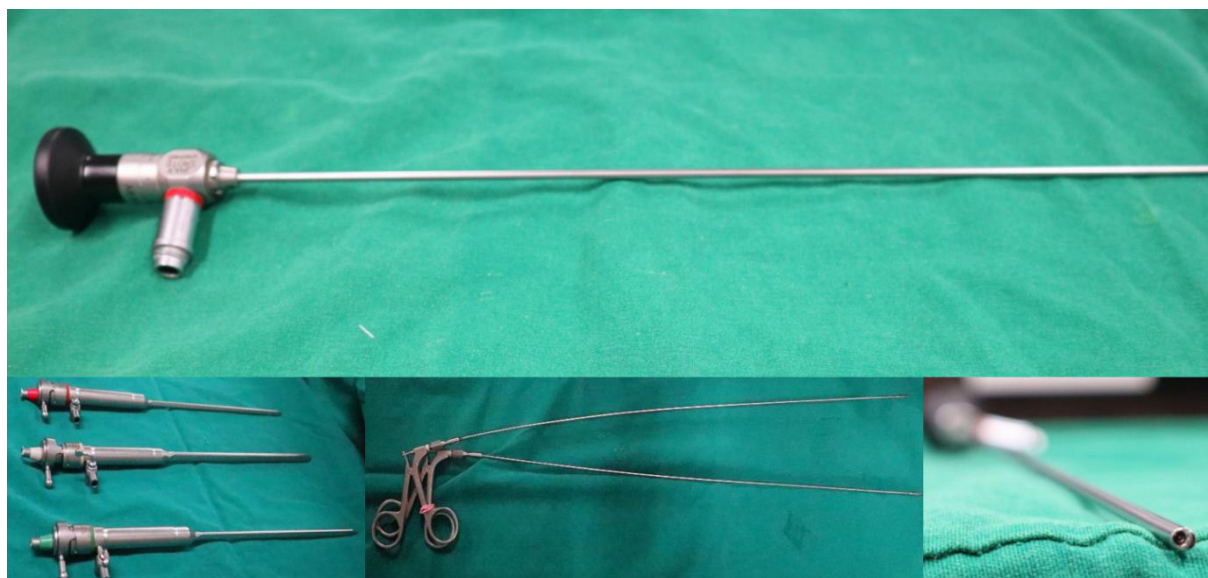


Figure 3. Decq scope and its tip with multiple channels and malleable instruments which can pass through it

Endoscopes and endoscopic procedures

In the 1990s, Claris Corporation was the first to come out with endoscope guided ventricular catheter placement for treating hydrocephalus^[12]. These scopes were lightweight, thin with outer diameter of 1.14 mm, and able to be introduced into shunt catheters. Medtronic Company from USA then came out with a similar functioning NeuroPEN endoscope. Correspondingly, slit tip catheters were introduced by Medtronic and Codman (USA) for ventriculoscopic placement. However, they did not attain wide acceptance as the literature consists of experiences mentioning only small case series^[13]. This was probably due to the absence of any discernible benefit over routine shunt catheter placements^[14], relatively higher costs, and suboptimal vision. However, neurosurgeons have not been deterred from probing avenues for further improvements in endoscopic treatment of hydrocephalus^[15]. The multipurpose ventriculoscope described by Henry Schroeder in 2008 helps in tackling not only obstructive CSF pathways but the extra channel allows also intraventricular lesion biopsy and resection, among other uses ably aided by the then newly developed high definition (HD) visualization and display system^[16,17].

Bauer, Hellwig, and their team from Marburg, Germany published their eight years of experience of stereotactic endoscopy^[18] wherein they used it for cystic cerebral pathologies, intracerebral hematoma evacuation, brain abscess, third ventriculostomy, and retrieval of ventricular catheters. Axel Perneczky^[19] from Mainz, Germany is credited with bringing “minimally invasive neurosurgery” to the mainstream in 1998 by greater use of narrower (MINOP, Aesculap) endoscopes in ventricles and using them for indications beyond hydrocephalus. He brought stereotaxy and navigation guidance in endoscopy to the forefront^[20] and developed the concept of “endoscope guided surgery” for cases such as colloid cysts. Endoscope assisted microneurosurgery was the next stage in the mid-1990s and innovations to attain the best dual imaging were highly sought after. Axel Perneczky proposed projection of the endoscopic images into a head mounted LCD device which was not routinely available in that period^[1]. His most important contribution was the concept of “keyhole surgical approaches” with the integration of these visualization methods to the skullbase and development of specially designed shaft instruments for dissection [Figure 4], clip applicators, and a table mounted endoscope holding device to aid bimanual endoscopic surgery.

Endoscopic third ventriculostomy (ETV) is one of the most widely performed procedures in neuroendoscopy today and its results have been validated worldwide for hydrocephalus^[21]. Several techniques and



Figure 4. MINOP shaft instrument with multiple attachments

instruments have been described for safe perforation of the ventricular floor and then dilating it, such as with the leucotome, puncturing needle, blunt endoscope, Fogarty balloon, monopolar electrode, wired stone extractor, *etc.*^[22]. Andre Grotenhuis from the Netherlands designed an endoscopic perforator which sucks and lifts the floor before forceps can be introduced to widen the opening^[23]. This reduces the chances of basilar artery damage during ETV. Success score systems predicting ETV's outcome in adult and pediatric patients^[24] and other criteria for defining its prognosis have been well explained in the literature^[25]. ETV has also been attempted via a flexible scope through the lamina terminalis in cases of technical difficulty to perforate the floor via traditional route^[26]. Endoscopic biopsy has also been favorably evaluated^[27], and occasional resections of tumors are being reported by many centers^[28,29].

The first series of cases published of endonasal transsphenoidal approach was by Jankowski *et al.*^[30] from France who presented his experience in three cases of pituitary adenomas in 1992. Subsequently, Jho and Carrau^[31] from the University of Pittsburgh, USA successfully used nasal endoscopes for transsphenoidal pituitary surgery and published the first large series of 50 patients in 1997. Immediately following that, the concept of functional endoscopic pituitary surgery was mooted by Cappabianca *et al.*^[32] in 1998 from Naples, Italy, which gave a big push forward to endonasal surgery. Thereafter, the preference shifted to the more versatile binostril approach, especially after very good results of 800 cases were put forward by Kassam *et al.*^[33] from USA. Gradually, extended approaches to pathologies of the skullbase came to the fore with the improvement in skullbase defect repair techniques^[34,35].

A dedicated pediatric endoscope was developed by Oi *et al.*^[36] from Japan for Karl Storz (Oi Handy Pro endoscope). This system had a smaller working diameter and a 2-mm lens with malleable instruments and a pistol grip for easier holding [Figure 5]. It provides a narrower tract which is extremely important in infants and small children, not only to minimize brain damage but also to reduce the occurrence of postoperative CSF leaks. It is also recommended in cases where the foramen of Monroe is not large enough for safe passage of the larger adult scope.

Pediatric Lotta system from Karl Storz was conceptualized by Henry Schroeder who developed this HD visualization scope with narrow shaft and another one with a wider shaft for adults with an extra channel that can take in two instruments through two channels of the scope apart from the suction-irrigation port

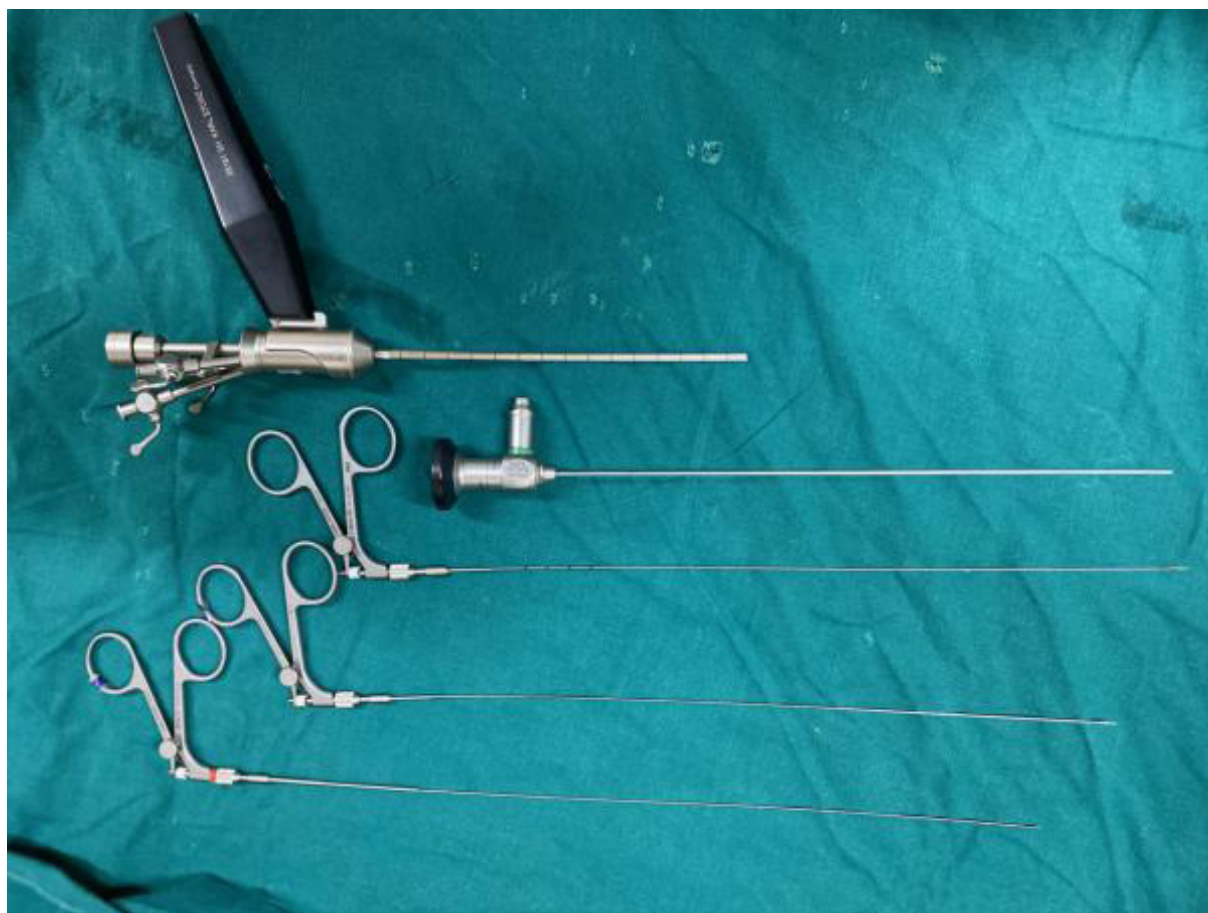


Figure 5. Oi scope with malleable instruments and pistol grip handle

[Figure 6A]. This system also has an optical obturator for scope insertion under visualization [Figure 6B]^[37]. Parallel developments in rigid endoscope were also undertaken by other companies such as Wolf from USA, Rudolf from Germany, and Olympus and Machida from Japan. The use of HD visualization has greatly improved accuracy of endoscopic neurosurgery and the recent introduction of 4K display system is a big stride forward in better visualization. Experience with 3D-HD endoscopy has slowly started gaining momentum in the field of neurosurgery. As compared to the traditional 2D display, 3D system provides a better depth perception especially for those neurosurgeons starting out in this field^[38]. This has still not come in wider use because of limited availability and much higher costs as well as due to the familiarity of most experienced neurosurgeons with dynamic endoscopy and 2D HD systems. Although this review focuses mainly on cranial endoscopy, a brief overview of spinal endoscopic system is given. One of the earliest innovators in spine endoscopic surgery was Destandau^[39] from France. By using the ENDOSPINE System (Karl Storz, Germany), he first described his technique for endoscopic discectomy in 1999, which is currently a widely practiced method. A versatile SMART endoscopic spine system was put forth by Chiu^[40] in 2006 with a wide variety of applications, viz. degenerative spine disease, spinal fixation, discectomy, *etc.* In 2007, Oertel *et al.*^[41] described the “EASY GO” system for spinal endoscopy consisting of dilators of varied sizes, sheaths, 30-degree endoscope, and endoscope holder. This system does not have a long learning curve and has been shown to have excellent postoperative response as per feedback of over 80% of patients.

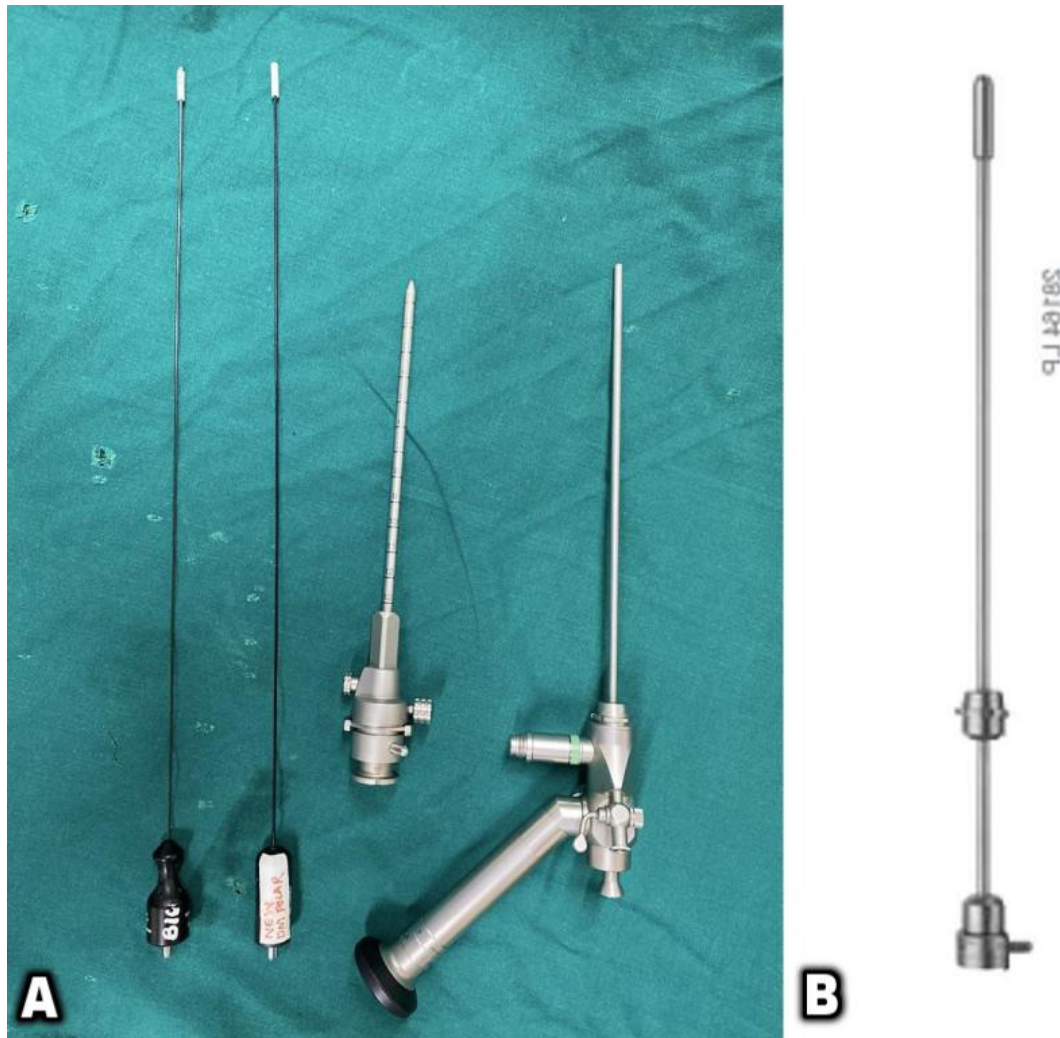


Figure 6. A: Lotta scope with ceramic bipolar; B: optical obturator for guided insertion

Endoscopic accessories

Irrigating sheaths for endonasal procedures

To improve visibility further and to tackle issues such as fogging in a better manner, lens cleaning devices and irrigating sheaths [Figure 7] were introduced by Cappabianca *et al.*^[42]. Although it may be extremely useful for better uninterrupted vision, especially without a good assistant, the increased outer diameter of the scope shaft with the sheath does not allow ease of instrumentation. We have favored dynamic endoscopy with manual irrigation. However, there are strong proponents of its use, e.g., Prof. Locatelli *et al.*^[43] with the forceful irrigation method called “diving technique”. This not only improves irrigation but also washes away debris forcefully and helps in developing better tissue planes by hydrodissection (waterjet method).

Endoscope holders

Endoscope holders add to the comfort and ease of the surgeon in endoscopy and help to free the operating hands [Figure 8]. The three types of holders available are rigid non-pneumatic (Aesculap), semi-rigid (Karl Storz), and pneumatic holders (Mitaka, USA)^[12]. The endoscope holders restrict your field of view and may be used for a small focused area of surgery, viz. ETV. However, the dynamic endoscope movement allows almost 3D visualization in endonasal approach, and hence holders are not preferred in that surgery. The

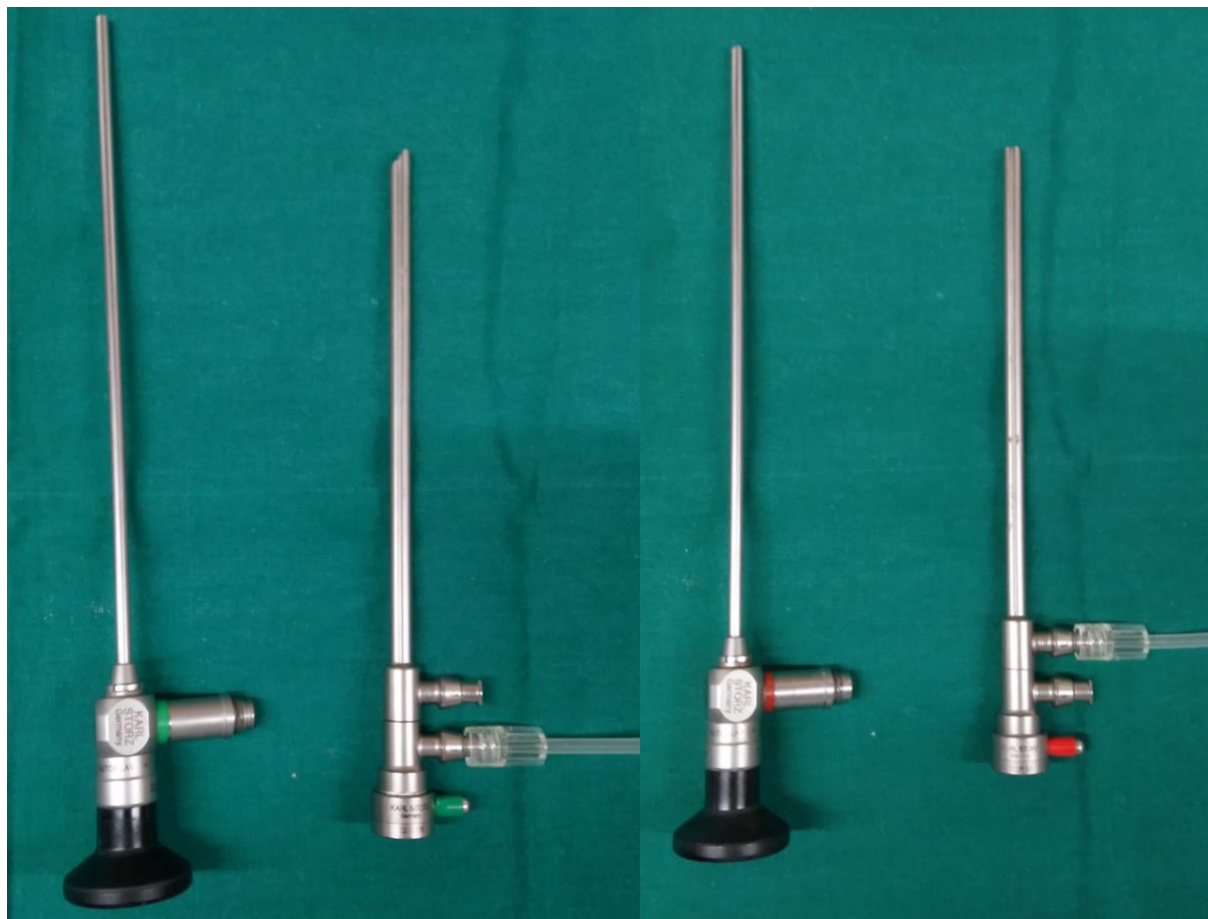


Figure 7. Nasal scope with irrigating sheath

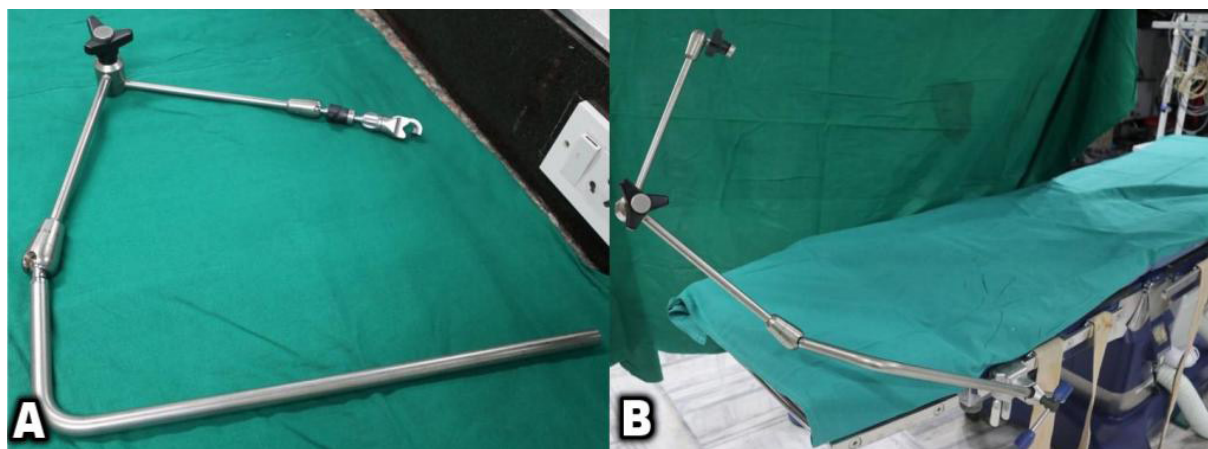


Figure 8. A: free endoscope holder; B: holder attached to the operating table

use of micromanipulator and holder with navigation may allow for fine controlled endoscope movement, as described by Lekovic and Rekate *et al.*^[44] in transventricular surgery for hypothalamic hamartomas.

Some of the other technological advances which have helped facilitate endoscopic surgeries include LASER, endoscopic ultrasonic surgical aspirators, neuronavigation, ultrasound probes, tubular retractors, bone ultrasonic surgical aspirator, robotic systems, and special drills.

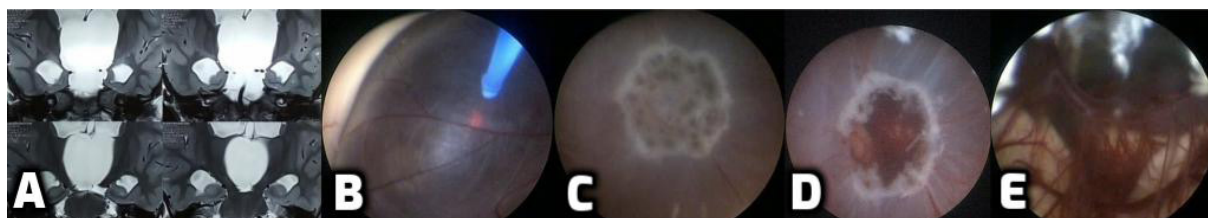


Figure 9. A: MRI T2W coronal section of giant suprasellar arachnoid cyst; B: coagulation of cyst wall by utilizing thulium LASER endoscopically; C: cyst wall after application of the LASER; D: perforated cyst wall; E: intracystic visualization after ventriculocystostomy

LASER

LASER application in neuroendoscopy has gradually evolved from the initial use of Nd:YAG and KTP LASER^[45,46] to the more recent introduction of Thulium [Figure 9], considered to be more precise and efficacious than its predecessors. Hypothalamic hamartoma disconnection by using thulium represents a good example of LASER replacing the conventional coagulation technique in neurosurgery^[47]. To combat the issues of damage to healthy brain tissue, LASER now consists of pretreated, carbon coated, diode fiber tip to prevent deeper neurovascular structures from getting damaged with the dissipating energy^[48].

Ultrasonic aspirator

Results of endoscopic ultrasonic aspirator use were first published in 2008 by Oertel *et al.*^[49]. Since then, it has been used for intraventricular [Figure 10] and paraventricular lesions along with thulium LASER for hemostasis^[50]. For endonasal surgeries, special thin and long tip ultrasonic aspirators can be used (Both ultrasonic aspirators by Soering, Germany). We have found ultrasonic aspirators to be useful but severe limitation can be faced due to repeated blockages and because it can only be used presently with Gaab endoscope channel. Barrow Institute from Arizona, USA introduced a variable aspirator and described its use for endoscopic resection of hypothalamic hamartoma in 2006^[44]. Numerous case series have since described the utility of a multipurpose side cutting aspirator (NICO, Myriad, USA) in neuroendoscopy especially in patients with intraventricular tumors^[51-54].

Navigation

Image guidance in neuroendoscopy has become a vital tool for planning and trajectory guidance [Figure 11] and has been proven to add value to some if not all procedures^[55]. A global survey of 235 neurosurgeons in 2012^[56] found that image guidance was used always in conjunction with intraventricular endoscopy by approximately 17% of participants, especially for tumor biopsy, resection, and cyst fenestration. When it came to endoscopic skullbase surgery, image guidance was used for all cases by 24% of respondents, and more so for recurrent and complex skullbase anatomy cases. Navigation has also been effectively combined with virtual endoscopy, i.e., magnetic resonance ventriculography, to help reduce chances of damage to critical structures during endoscopic surgery^[57]. Technically, the tool has advanced over years by overcoming the initial shortcoming of head fixation considered imperative for many years to achieve accuracy. There has since been development of navigation system with face mask (Stryker) and electromagnetic system by companies such as Medtronic, Brainlab, *etc.* Neither system requires the head to be fixed with pins during surgery. Today, neuronavigation also plays a significant role in simulation training for endoscopy in cadavers as well as synthetic models^[58,59].

Ultrasound

Ultrasound for navigation guiding neuroendoscopy procedures was described as early as the 1990s^[60,61]. This can be very useful if a child has an open fontanelle and is undergoing endoscopic treatment for complex hydrocephalus or multiloculated cysts [Figure 12] and is effectively used by many surgeons as an alternative to MR guided procedures^[62]. Intracranial application of ultrasound probes concurrent with

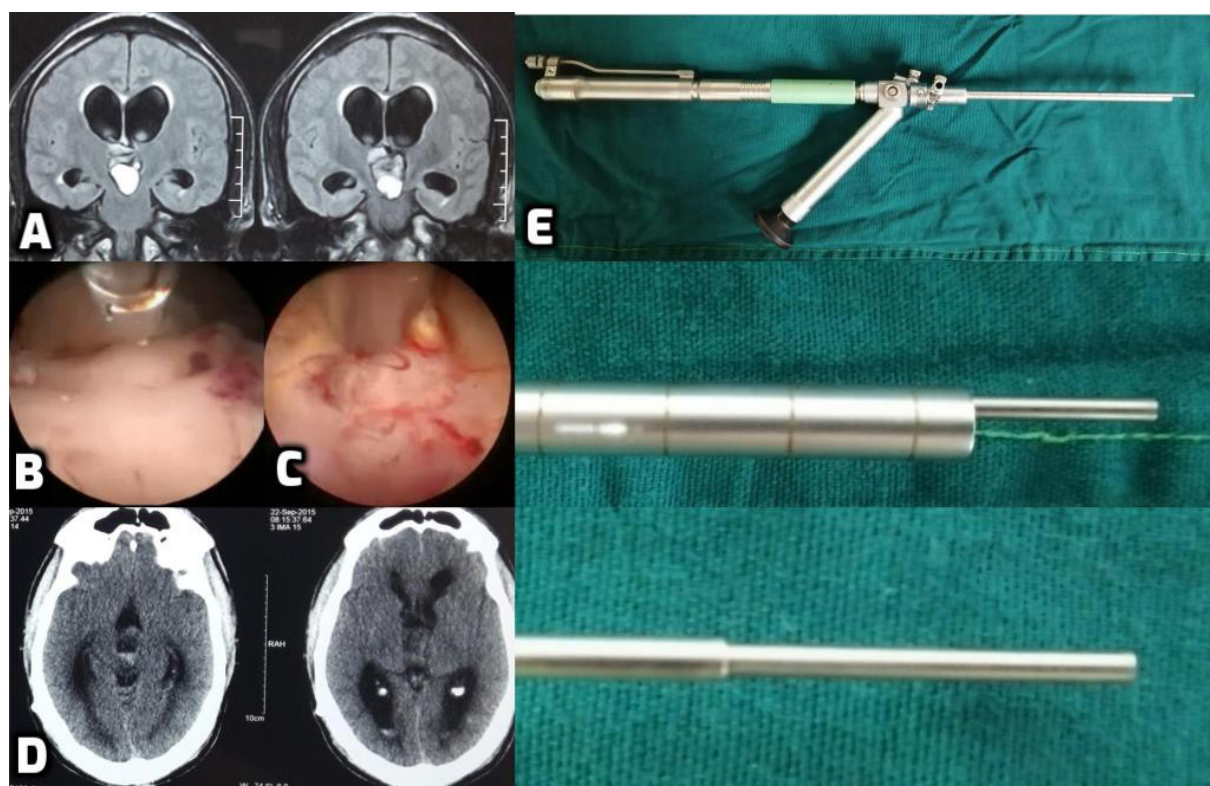


Figure 10. A: MRI FLAIR coronal section of an intraventricular solid cystic pilocytic astrocytoma; B: endoscopic view of the tumour; C: ultrasonic surgical aspirator applied for excision of the lesion; D: postoperative CT scan after gross resection of the lesion via endoscopic approach; E: ultrasonic surgical aspirator instrument with zoomed image of the tip

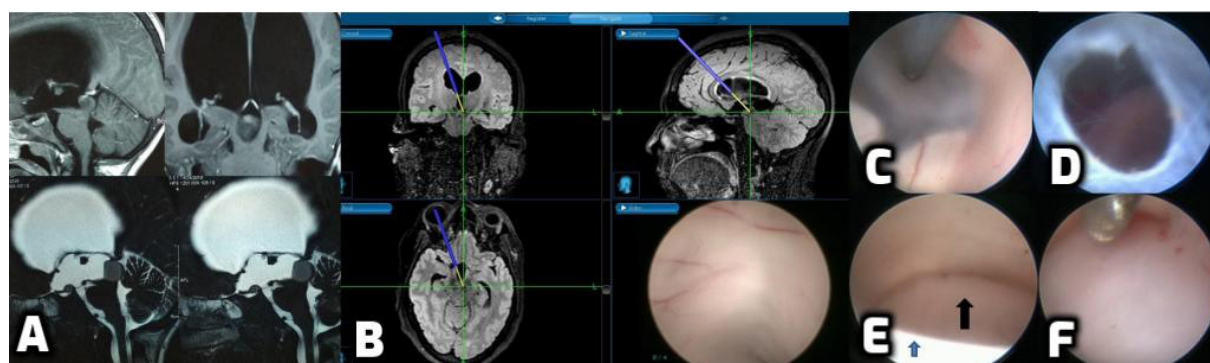


Figure 11. A: MRI (post contrast and T2WI) of a five-year-old child with pineal lesion and hydrocephalus; B: use of navigation to help in planning the trajectory intraoperatively; C: endoscopic third ventriculostomy done; D: basilar artery seen through the flapping ventriculostomy site; E: tumour (black arrow) seen anterior to the massa intermedia (blue arrow); F: the scope was negotiated below the massa intermedia to reach the tumour for biopsy

endoscopy has been described for hematoma evacuation, biopsies, ventriculostomies, *etc.*^[63-65]. Doppler technology of ultrasound has also been used in endoscopic surgeries to indicate presence of surrounding fine vascular structures, thereby increasing the safety profile of endoscopy^[66]. The utility of Doppler in endonasal surgeries, especially for invasive tumors, recurrences and extended procedures can be gauged by its widespread usage at several centers for lesions with intracavernous extension and carotid encasement^[67].

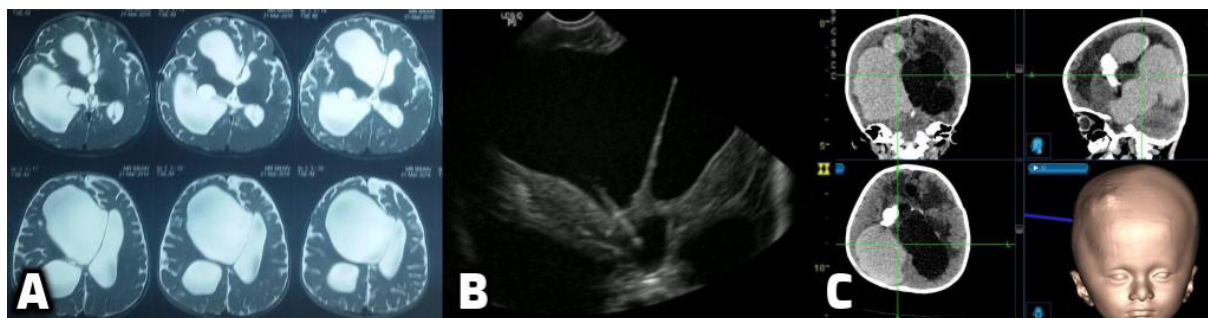


Figure 12. A: MRI T2W axial section showing multiloculated hydrocephalus; B: ultrasound image for guidance of septostomy; C: navigation image showing successful septostomy with passing of catheter to the opposite ventricle

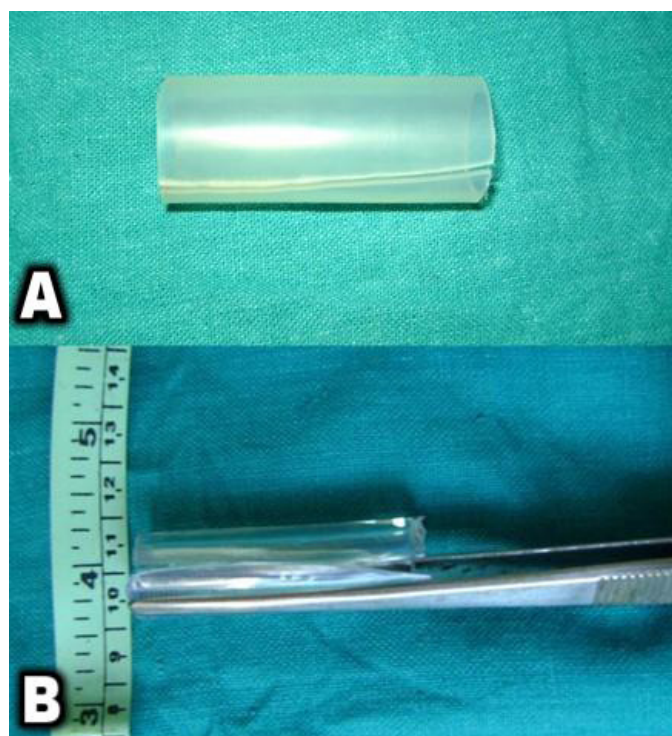


Figure 13. A: the tubular retractor designed by Yadav *et al.*^[70] in 2011. Longitudinal cut allows the retractor to be folded onto itself; B: the small size prevents a large cortical opening

Retractors

Tubular retractors represent another avenue of augmenting the minimally invasive nature of neuroendoscopy. For intraventricular lesions, a transparent cylindrical port was developed by Daniel Prevedello, Amin Kassam, and their group^[68]. Many series have been published elaborating on transparent sheath retractor use for ventricular tumors including syringe ports^[69]. We have used simple transparent tubes for some years now for deep seated lesion excision, while Yadav *et al.*^[70] used it with a small slit to reduce pressure on surrounding brain [Figure 13]. Tubular retractors have also been modified for use as a nasal retractor in skullbase endoscopic surgery^[71]. Even though the field of vision is proven to be better with microscope assisted surgery than neuroendoscopy^[72], many surgeons still favor these retractors.

Hemostats

Hemostasis aiding endoscopic surgery still relies greatly on conventional and long existing methods such as copious warm irrigation, absorbable gelatin sponges (Gelfoam from Baxter), and oxidized regenerated

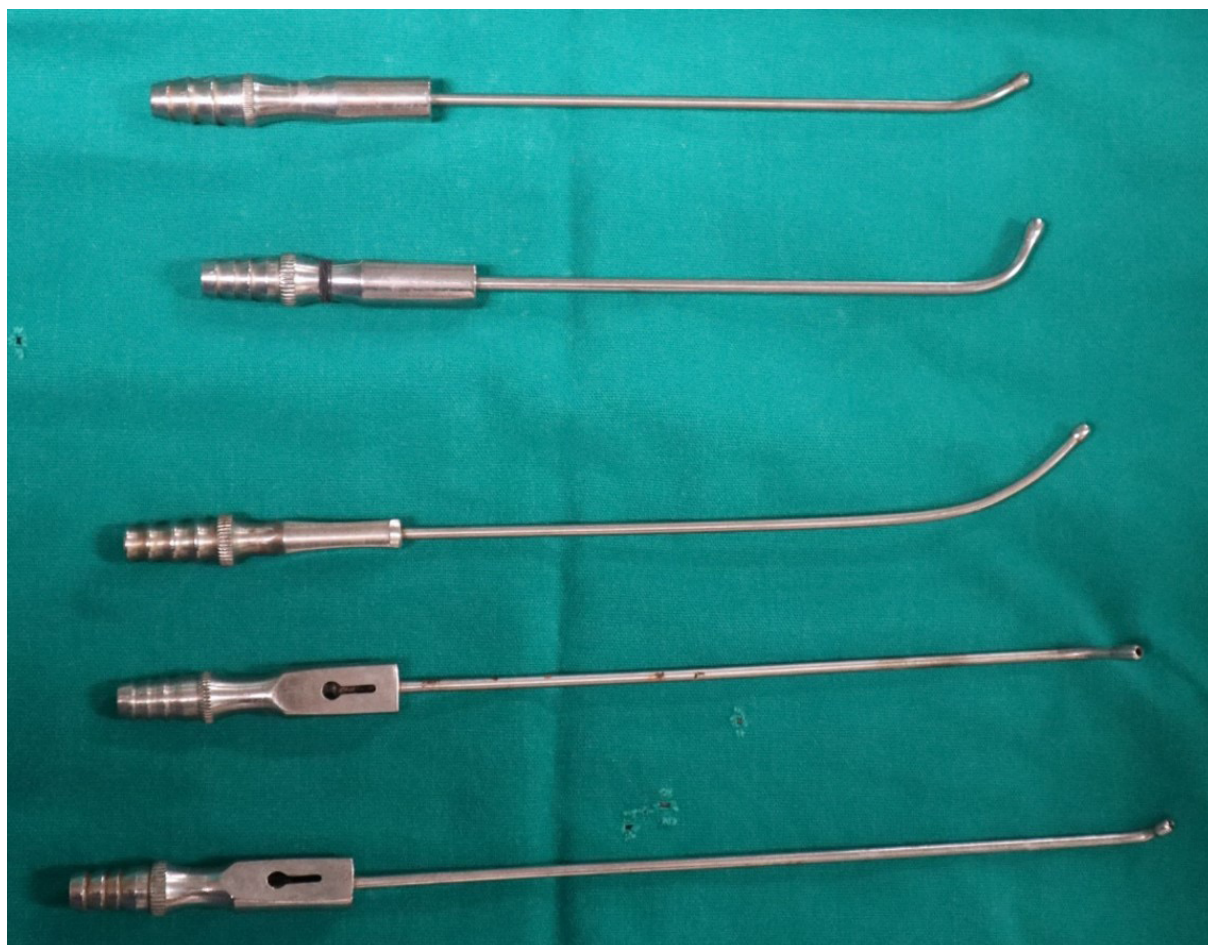


Figure 14. Angled suction tips for cavernous sinus and other areas

cellulose (Surgicel from Ethicon). Newer hemostats have also been introduced with proven benefit in neuroendoscopy such as fibrin sealant (Tisseel from Baxter, Evicel from J&J) and gelatin-thrombin matrix sealant (FloSeal from Baxter)^[73,74].

Specialized instruments

Ergonomically designed instruments for endonasal surgeries include concealed retractable knife, rotatable scissors for dural incision, curved keyhole and non-keyhole graded suctions, disc dissectors, fine dissectors, ring curettes of varying angles for tumor separation, and pistol grip endoscopic bipolars which can be rotated to adjust the axis of the distal cauterizing tips into a horizontal or vertical plane. Neurosurgeons contributing with instruments for facilitating skullbase endoscopy include Amin Kassam's specialized bipolar and suction device^[75] and Paolo Cappabiancas' retractable knife. We have developed our own angled suction sets [Figure 14], malleable keyhole suction and malleable silver dissector [Figure 15], curettes [Figure 16], and bipolar forceps without sliding movement [Figure 17], as shown in Figures 15-17.

Shuntoscope and new fiberoptic scopes

Semi rigid shunt scope systems [Figure 18] by Karl Storz, Germany have been shown to achieve a more accurate catheter placement, especially in pediatric patients with slit ventricles^[76]. The next generation fiberoptic neuroendoscopy with "chip on tip" camera combines the best of both flexible and rigid scopes. They were originally developed for bronchoscopy and provide excellent visualization and flexibility to work in the lamina terminalis, temporal horns, fourth ventricle, etc., which are not easily accessible by rigid



Figure 15. A: malleable keyhole suction; B: malleable silver tipped dissector

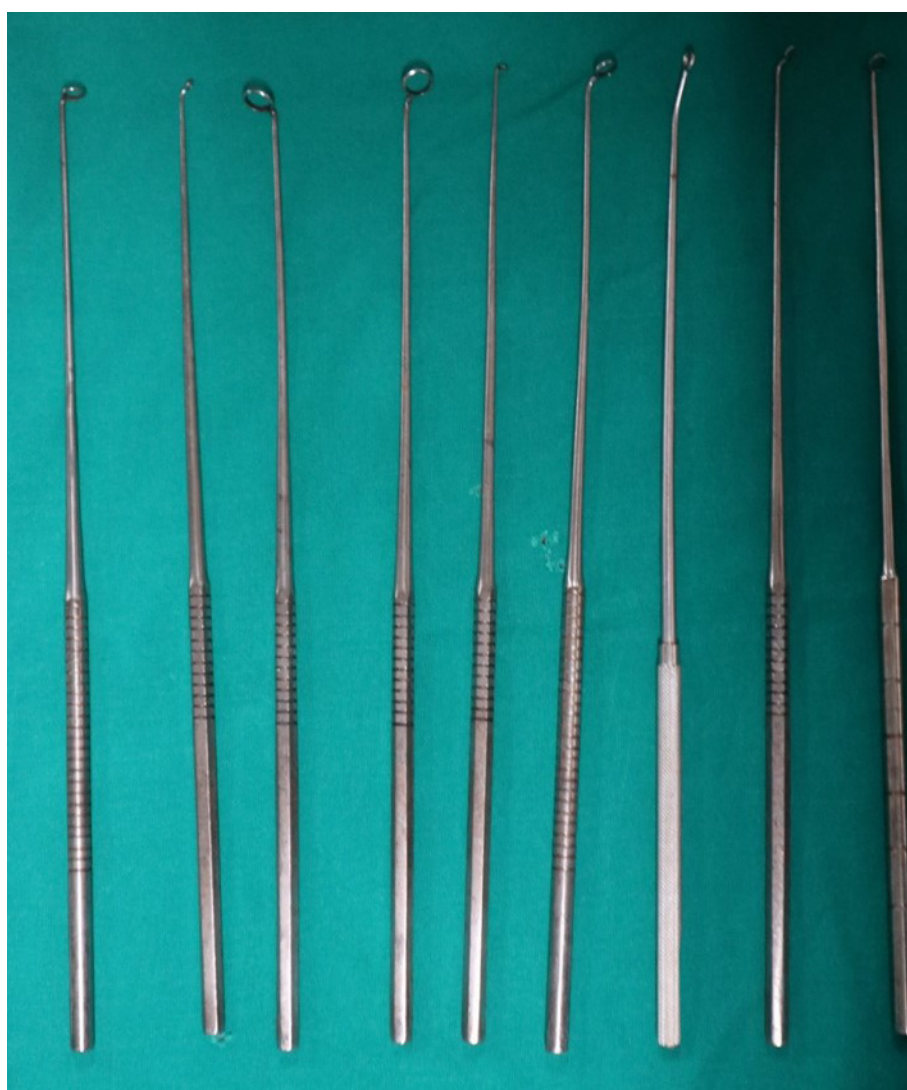


Figure 16. Curettes with various angled tips

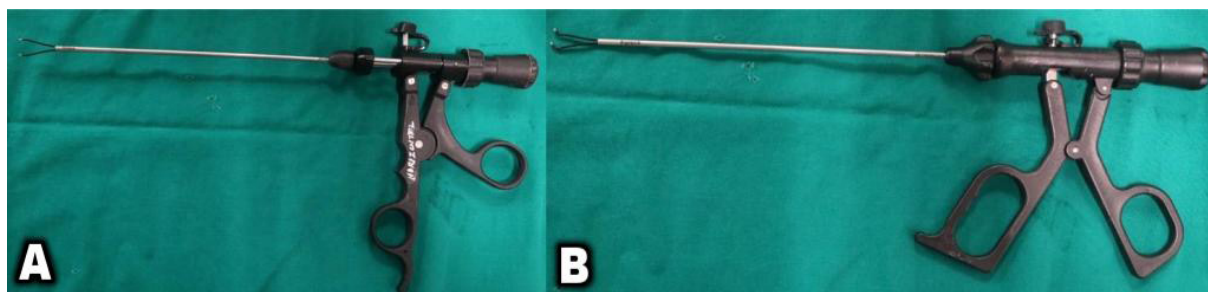


Figure 17. A: bipolar forceps with horizontal tip; B: bipolar forceps with vertical tip

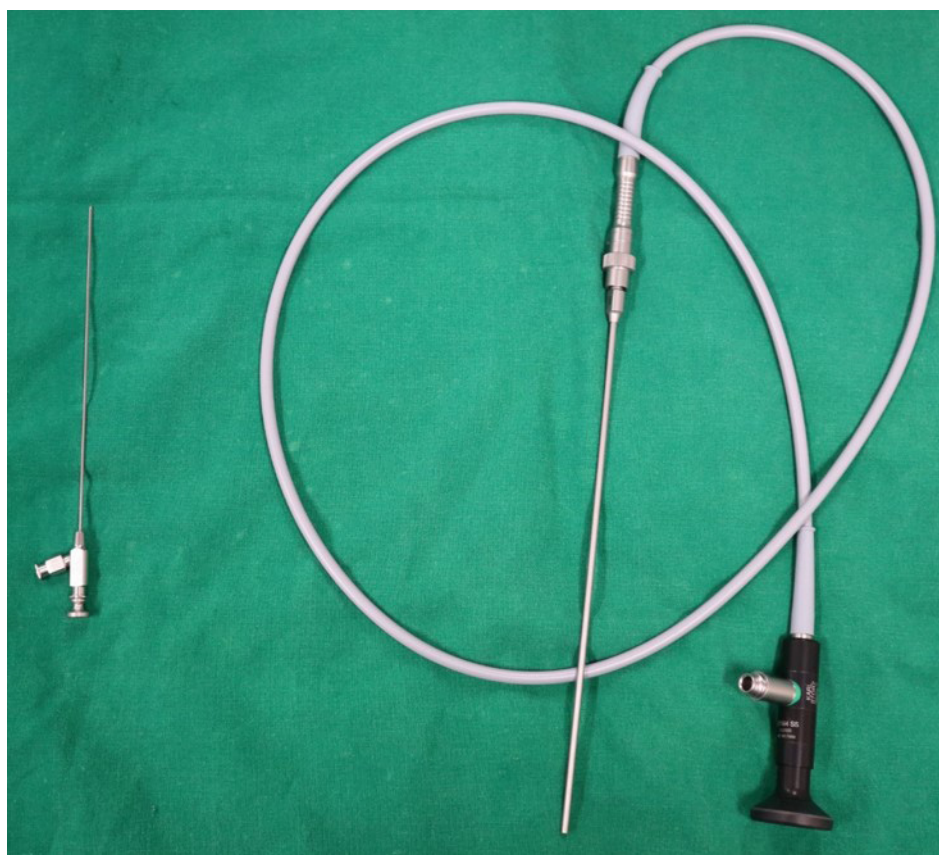


Figure 18. The shuntscope system

scope^[77]. Currently, they are more expensive than the traditional rigid endoscopes, and there have been reports of visual and electrical interference when used concurrently with monopolar cautery^[78]. There is also the problem of their sterilization process to ensure safety.

Scope and potential

Today, the scope of endoscopy has expanded to craniosynostosis repair^[79], carpal tunnel release (where it has been found to reduce the immediate postoperative pain as compared to open surgery)^[80], and endonasally for clipping suitable aneurysms such as unruptured paraclinoid, anterior communication artery, and basilar apex aneurysms^[81]. A crucial role played by endoscopy in vascular surgery is inspection behind the aneurysms to see origin of a hidden branch or important perforators increasing safety of clipping and assuring a complete clipping.

Robotic Neuroendoscopy

The first application of robotic systems in neuroendoscopy was in 2002 by Zimmermann *et al.*^[82] when they successfully used Evolution 1 robot for navigated robotic neuroendoscopic procedures in three patients. Since then, the robotic stereotactic assistance system has been used at many institutions for endoscopic third ventriculostomies, among other procedures^[83,84]. Robotic guidance systems will eventually provide greater precision, vision, and stability in neuroendoscopy^[85]. However, as of today, the primary practical role of robotics in neurosurgery is of visualization, to add greater degrees of freedom onto the existing rigid endoscopes along with providing navigation modality for procedures such as biopsies. The surgical component of neuroendoscopy remains under manual control.

Going ahead, it seems almost inevitable that smartphones may soon play an important adjunct role in neuroendoscopy given their widespread availability and uniformity in the operating systems. They have already been touted to replace the video screen system once deemed to be essential along with the endoscope set^[86]. By amalgamating the light source and camera into a single cable and by reducing the overall weight of the traditional endoscope, Karl Storz came out with a prototype multifunctional videoendoscope which can effectively be used as a single-handed instrument with ease^[87]. Early results are encouraging in terms of both navigating the instrument and the high-definition images it provides.

A contemporary classification has been proposed in the last few years for endoscopy in minimally invasive cranial neurosurgery taking into consideration its vast application and potential. The procedures can now be grouped as “intraendoscopic” or “extraendoscopic” based on the relation of surgical exercise with the axis of the endoscope^[88]. This expands the scope of MIS beyond the traditionally defined realms.

Training models and programs

Currently, many training modules have come to the fore providing young neurosurgeons with experience and practice of life-like clinical scenarios. Apart from computer graphics helping ventricular and endonasal surgeries, synthetic models have also been developed which have been proven to improve hand-eye coordination in endoscopy and reduce the training curve usually associated with it^[89]. We have developed a model for ventricular surgery which has been very popular with the young trainees^[90]. Skullbase endoscopy training, however, is best served with cadaveric training and such courses are being regularly held at several conferences, universities, and training centers [e.g., University of Pittsburgh, USA, and Center of Excellence for Minimal Access Surgery Training (CEMAST), Mumbai, India], *etc.*

CONCLUSION

Neuroendoscopy is integral to development of minimally invasive neurosurgery. Apart from development of alternative procedures such as endoscopic third ventriculostomy, which have become standard of care, its use has become widely prevalent in transsphenoidal pituitary surgeries as well. It has also opened the doors for extended procedures in skullbase tumors and ventricular tumors. With time, the use of smartphone navigation, robotic applications, and exoscopes in endoscopy will augment the existing armamentarium in neuroendoscopy. Further advances in visualization methods will guide future progress of minimally invasive neurosurgery.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation, performed data acquisition, as well as provided administrative, technical, and material support: Shaikh S, Deopujari C

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Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Editorial

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Searching for a better definition of robotic surgery: is it really different from laparoscopy?

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Although both laparoscopic surgery and robotic surgery are minimally invasive techniques, the hope for robotic surgery is that it represents an evolution of minimally invasive technology that will improve the precision of surgeons movements in ever increasingly narrow and small anatomic spaces. It is widely believed that robotic technology works as a filter for the involuntary tremors of the surgeon, theoretically resulting in a minimization of involuntary inaccuracies, thus helping surgeons to further perfect their art. That robotic surgery is a natural evolution of minimally invasive surgery is not questioned; however, the veritable explosion of robotic enhancement begs the questions: Are all surgical robots created equal? What should be considered robotic surgery and what should be considered robot-assisted?

The meaning of the words robot and robotics are surprisingly complex. The etymology of robot comes from the Slavic word “robot” that means servitude, servant, and disturbingly slave. It first appeared in print in 1920 in the play R.U.R. (Rossum’s Universal Robots) about a factory that makes androids and was written by the Czech writer Karel Čapek^[1]. Isaac Asimov is then credited with coining the term robotics in a short story titled “Liar!” that was first published in 1941^[2]. Since then, the term robot has taken on a number of meanings with its main definition being a machine or device that does the work of a human either autonomously or under computer control.

Robotics has become a field of engineering that utilizes computer science to design, manufacture, operate, and utilize robots. It has become an interdisciplinary field that uses aspects of electronic, computer, mechanical, and information engineering. The field of robotics has innumerable potential applications,



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Figure 1. A: da Vinci complete surgical robotic systems have three major components: (1) the surgeon's console; (2) a surgical cart with the robotic arms and end-effectors; and (3) the visual cart (copyright Intuitive Surgical International - reproduced courtesy of the manufacturer); B: the latest iteration of the surgical cart for the da Vinci Xi Surgical System (da Vinci, Intuitive Surgical, Sunnyvale, CA, USA)

but it has been divided into five broad fields: sensors, programming, mobility, human-robot interface, and manipulation. It has also been divided into four broad divisions: bio, industrial, mobile, and aerial. Currently, robotic surgery would seem to fall in the bio division and mainly in the field of manipulation. Perhaps the clearest definition of robots is the one published by the American Institute of Robotics in 1979, "a robot is a reprogrammable, multifunctional manipulator designed to move material, parts, tools, or specialized devices through variable programmed motions for the performance of a variety of tasks"^[1].

Although the da Vinci robot (da Vinci, Intuitive Surgical, Sunnyvale, CA, USA) has come to dominate the field of robotic surgery [Figure 1], the field of robot-assisted surgery was initially popularized with the robotically-controlled laparoscope holder AESOP (Computer Motion, Inc., Sunnyvale, CA, USA) in



Figure 2. The AESOP robotic laparoscope holder (Computer Motion, Inc., Sunnyvale, CA, USA)

the mid-1990s^[3] [Figure 2]. This device was so well-liked that it became a victim of its efficacy, and the company was purchased by Intuitive Surgical and promptly shelved, thus eliminating any competition. Nonetheless, this remote-controlled robot is widely considered the first robot used in minimally invasive abdominal surgery, yet surgeries done with it are not even considered robotically-assisted procedures by most surgeons.

Another robotically-controlled laparoscope holder called ViKY (short for Video-endosKopY; ViKY, Endocontrol, Grenoble, France) then came on the market^[4] [Figure 3]. Unlike AESOP or the da Vinci, this robotically-controlled laparoscope holder is autoclavable and can be sterilized. Endocontrol then developed hand-held 'robotic' instruments that have additional degrees of articulation that are really just motorized laparoscopic instruments (JaiMY, Endocontrol, Grenoble, France)^[5] [Figure 4]. These two devices were developed so that surgeons could overcome the loss of haptics that exists with the da Vinci Robot, specifically the loss of the sensation of touch. Other hand-held instruments with end-effectors and increased degrees of freedom exist; however, unlike JaiMY, these devices are fully powered by the force of the surgeon and have no powered motors.

Robotic surgery is traditionally defined as any surgery done with a complete robotic surgical system. Up until recently, the only complete system was the da Vinci Surgical System [Figure 1]. It was originally developed for the military so that surgeons could remotely do open surgery on wounded soldiers in the field; the device was retrofitted for minimally invasive surgery as this was more marketable. During these



Figure 3. VideoendosKopY (ViKY) robotically-controlled laparoscope holder (ViKY, Endocontrol, Grenoble, France)



Figure 4. Articulating 5-mm laparoscopic instrument with motorized control (JAIMY-EN, Endocontrol, Grenoble, France)

procedures, a surgeon sits at a console several feet away from the patient, and the motorized effector arms of the robot are the ones in actual contact with the patient^[1]. The operating surgeon is not wearing a sterile gown or gloves and only the robotic arms and surgical assistant are in contact with the patient. A telemanipulator is a remotely-controlled device that enables the surgeon to control surgical instruments using manipulators and motorized end-effectors. During the Lindbergh Operation in 2001, when the first Trans-Atlantic minimally invasive surgery was done, a telemanipulator was also used, but an additional computerized system was necessary to control the end effectors and robotic arms across such a great distance^[6].

The bright future of complete surgical systems is perhaps best highlighted by the development of competitors to the da Vinci robot. The Versius robot (Versius Robotics, CMR, Cambridge, UK) has a computer interface to enable haptic feedback [Figure 5]. A notable weakness of the earlier da Vinci robots

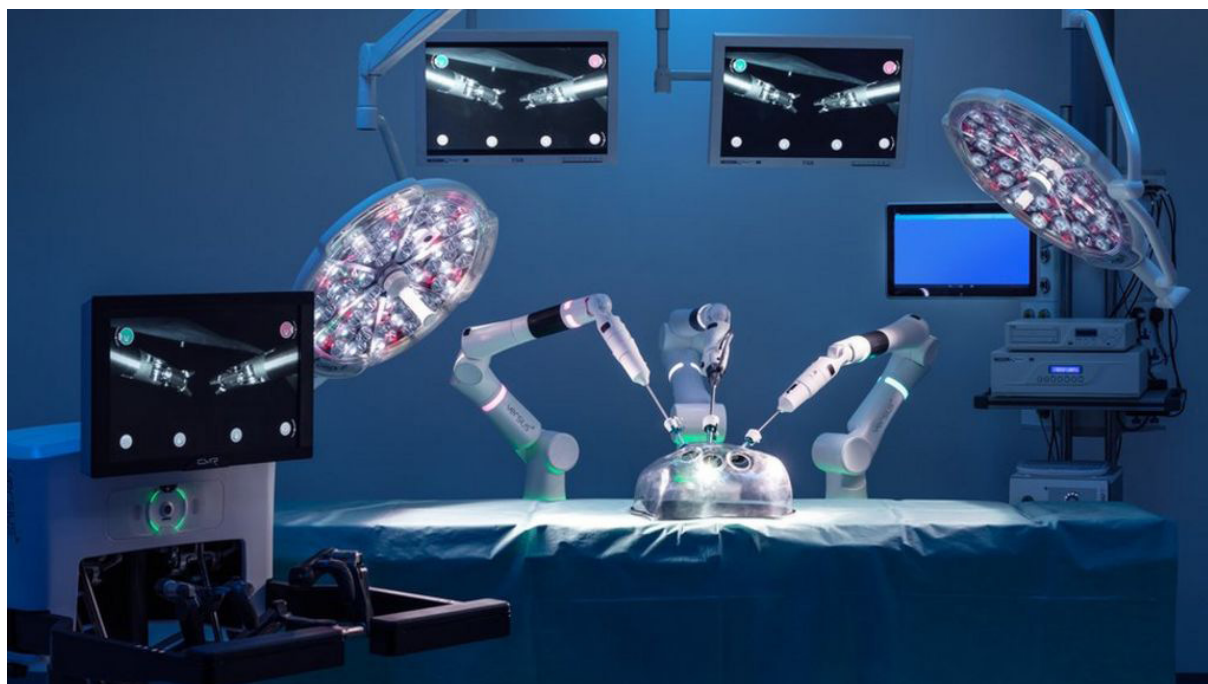


Figure 5. The Versius complete surgical system with surgical console, robotic arms, and laparoscopic tower (Versius Robotics, CMR, Cambridge, UK)

and one of the main reasons certain minimally invasive surgeons have not embraced this technology is that they are waiting for a robot with haptics^[7]. Notably, the initial generation Versius will also not have haptics^[8,9]. Medtronic, one of the largest surgical instrument companies, has even developed a complete surgical system called Hugo (Hugo Robot, Medtronic Inc., Dublin, Ireland).

With the general surgeon's current definition of robotic surgery, the robot is not autonomous and does not perform any actions automatically. Instead, the instruments move either through the action of a telemanipulator with motorized end-effectors or through computer control. In short, robotic surgery seems to fall well short of the definition proposed by the American Institute of Robotics^[1]. On the contrary, in spinal surgery (Mazor Robotics, Mazor Robotics, Inc., Caesarea, Israel), radiation therapy with the Cyberknife (Cyberknife System, Sunnyvale, CA, USA), and head and neck surgery (Flex Robotics System, MedRobotics, Raynham, MA), there are several robots that also have some degree of automation^[2,10-12]. Ultimately, it must be remembered that the logical conclusion of developing robotic surgery will probably result in either partial or total automation of operations even in general surgery.

Another reason that the term robotic surgery is difficult to define is that several devices used in abdominal surgery have automatic motorized components. There is a hand-held stapler called the iDrive (iDrive, Medtronic Inc., Dublin, Ireland) with automatic motorized stapling that if used could technically define a procedure as being robotically-assisted [Figure 6]. Theoretically, an open colectomy where a surgeon uses the iDrive could be considered a robotically-assisted procedure. Furthermore, although some so-called robotic cases use a complete "robotic" surgical system for the majority of the procedure, some procedures use a hybrid approach. For instance, should a minimally invasive esophagectomy that had its abdominal portion done laparoscopically, but the thoracic portion done with the da Vinci robot, be considered robotic, robot-assisted, or is minimally invasive a better term? Is there a percentage of a case that needs to be done with the robot before it should be considered laparoscopic, robotic, or robot-assisted? What about robotically-assisted Whipple procedures where the pancreatic head resection is done laparoscopically,



Figure 6. Automatic motorized gastrointestinal stapler device (iDrive, Medtronic Inc., Dublin, Ireland)

but the reconstruction is done robotically or vice versa^[13]? What if the reconstruction is done through a mini-laparotomy? If a robotically-controlled laparoscope holder is used for a totally laparoscopic Whipple procedure should it be considered robotically-assisted^[14,15]?

Notably, new techniques of hernia repair that obviate the need for entering into the abdomen at all such as the Trentino Hernia Team (THT) technique may make the robot superfluous for many midline hernia repairs^[16]. Currently, open surgery is still the fundamental foundation of abdominal surgery regardless of the approach used, particularly for the management of catastrophic injuries and complications. As a result, in this Special Issue, some authors will discuss the management of certain sequelae and/or complications of robotic and laparoscopic minimally invasive surgery that cannot currently be managed minimally invasively. This highlights the possibility that, although some general surgical procedures, such as ileostomy takedown, can never be done minimally invasively, they could theoretically be done with the aid of a robot. The original impetus for the da Vinci cannot be ignored: engineers wanted to create a robot that could do even open surgery, and surgeons must be prepared for the possibility that one day this may become a reality. This possibility is made more clear when we consider that robots designed to function as scrub nurses have already been developed^[17].

Currently, the complete surgical “robotic” systems seem to be more of a “motion-control” system and not a fully robotic or “reprogrammable” surgical system^[2]. Nonetheless, these complete systems will continue to be beneficial for surgeons, particularly for pathology in small spaces such as the pelvis, which has been elucidated by the explosion of robotic radical prostatectomy. With the continued evolution of robotic platforms such as the da Vinci Single-Site Platform (da Vinci Single Site Technology, Intuitive Surgical, Sunnyvale, CA, USA) [Figure 7], it is impossible to deny the future potential of robotic surgery. This collection of invited manuscripts from international leaders in the field of robotic and laparoscopic surgery

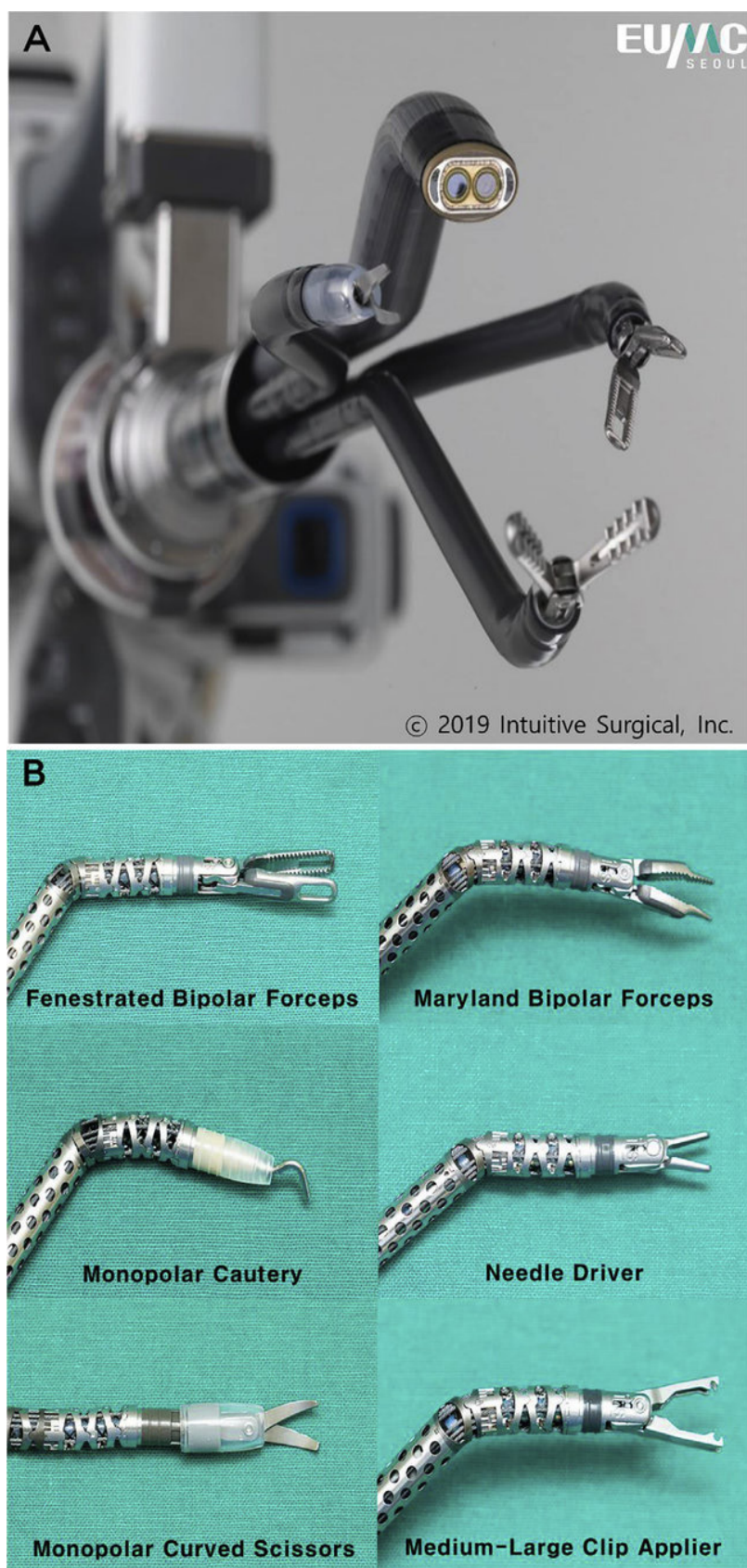


Figure 7. A: da Vinci Single Port (SP) arm (da Vinci, Intuitive Surgical, Sunnyvale, CA, USA); B: available instruments for the da Vinci SP (da Vinci, Intuitive Surgical, Sunnyvale, CA, USA)

will hopefully shed some light on the question as to what the relevant definition of robotic or robot-assisted surgery should be. It is increasingly clear that surgeons will need to be fluent in open, laparoscopic (including endoscopic and thoracoscopic), and “robotic” techniques, and that all three of these modalities are simply what it means to be a modern surgeon.

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Editing and provided administrative support: De Simone B, Chouillard E

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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Robotic liver surgery: literature review and current evidence

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Abstract

In the field of minimally invasive surgery, robotic surgery (RS) was introduced to overcome drawbacks in laparoscopic surgery. However, its clinical application in hepatobiliary surgery is not yet standardized. This review analyzed the results of RS to clarify the benefits of robotic liver surgery in comparison with standard laparoscopy. Among 112 publications found in the literature, the 72 most relevant were selected and the following data were extracted: patients characteristics, operative procedures, histopathology, short-term and long-term outcomes, and costs. Twenty-nine articles on robotic liver resections, published in the last five years (2015-2020) and including 1831 patients, were analyzed. Twenty-five comparative studies between robotic and laparoscopic surgery were evaluated to underline the differences in operative outcomes. Eventually, 4 sub-group analyses were conducted on hepatocellular carcinoma, gallbladder cancer, hilar cholangiocarcinoma, and colorectal liver metastases. Almost all the authors reported data on safety, feasibility and oncologic effectiveness of RS reaching comparable results with laparoscopy. However, even if robotic surgery showed longer operative time and higher costs, in selected cases it allowed to increase the rate of minimally invasive approach when compared with laparoscopy. Thus, both open and minimally invasive surgery should be provided in a modern hepatobiliary center, including the robotic approach particularly to complex cases, otherwise very demanding by laparoscopy. In conclusion, different techniques should be tailored to each patient, choosing the minimally invasive approach when possible, enhancing patients' recovery after surgery, especially in cirrhotic livers and in the context of liver transplantation. Although many centers experienced robotic liver surgery, more and larger studies are necessary to define its real benefits relative to laparoscopy, in order to standardize patient selection criteria and techniques.



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Keywords: Robotic liver surgery, robotic liver resections, laparoscopic liver resections, hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, colorectal liver metastases

INTRODUCTION

Since its introduction, robotic surgery (RS) has received great interest from scientific societies. In the era of minimally invasive surgery (MIS) it represents an advanced technique able to overcome some limitations of laparoscopy. Nevertheless, its use is not standardized in hepatobiliary surgery. Although single surgeons and centers have published their experiences demonstrating the safety and feasibility of the technique, large international studies are limited and few publications reported long-term outcomes. The advantages of RS are several: it provides increased surgical dexterity and enhanced suturing ability, thanks to a magnified three-dimensional view of the operative field, hand tremor filtration and articulating instruments with seven-degrees of freedom. Furthermore, this approach reduces significantly surgeons' fatigue, improving performances for long operations^[1,2]. In addition, RS supports and upgrades the technology of specific surgical tools, that can help surgeons to face challenging situations and improve surgical results, such as with intraoperative ultrasound, near-infrared fluorescence with indocyanine green, CT and MR images integrated into the robotic console. The images can be simultaneously displayed with the operative field during liver parenchymal transection, allowing the surgeon to change the previously marked transection line if necessary and to detect further lesions, gaining adequate margins for malignancies^[3-5]. On the contrary, current RS systems' disadvantages include the absence of a dedicated instrument for transection (i.e., CUSA), the need for additional surgeons and time for instrument replacement, the learning curve of the team to dock the instruments and the lack of haptic feedback^[2]. Nonetheless, the development of skills and experience of the surgical team can significantly decrease the length of RS associated to the docking time and the replacement of the instruments^[6]. Finally, one of the major drawbacks of RS are costs, limiting its use to selected surgical procedures and few centers. As a minimally invasive approach, RS allows improvement of almost all the parameters of postoperative recovery, such as pain control, oral intake, post-operative morbidity and length of hospital stay^[7]. Recently, the Southampton international guidelines, providing indications and limits of liver MIS, advocated RS as a promising, but not yet standardized, approach^[8]. The aim of this review was to analyze the results of robotic hepatobiliary surgery and to compare them with laparoscopy, in order to clarify the benefits and contraindications of RS.

METHODS

A search of the current literature on robotic liver surgery was conducted in PubMed, Medline, PMC and Google Scholar databases. The research terms adopted were: robotic/robot-assisted liver surgery/resection, hepatic robotic surgery/resection, robotic/robot-assisted hepatectomies. Only articles published in English were selected. Further reports were retrieved from those listed in the articles' references and from the manual search on specific additional topics, such as robotic surgery for hepatocellular carcinoma, cholangiocarcinoma, gallbladder cancer, colorectal liver metastases, lesions located in postero-superior liver segments, comparison between laparoscopic and robotic hepatic resections.

Among the 112 publications analyzed, the most significant were selected according to the following factors: quality of data reported and of statistical analysis adopted, relevance in scientific literature, date of publication. In case of overlapping studies with the same first author, the most recent was chosen. Once reviews, meta-analyses and studies reporting incomplete or unclear information were excluded, the following data were extracted from the 72 remaining publications: patient characteristics (number of patients, age, sex, body mass index, ASA score, comorbidities, previous chemotherapy and abdominal surgery), operative procedure (type of resection, use of Pringle maneuver, additional simultaneous procedures, intraoperative drain placement, estimated blood loss, operation time,

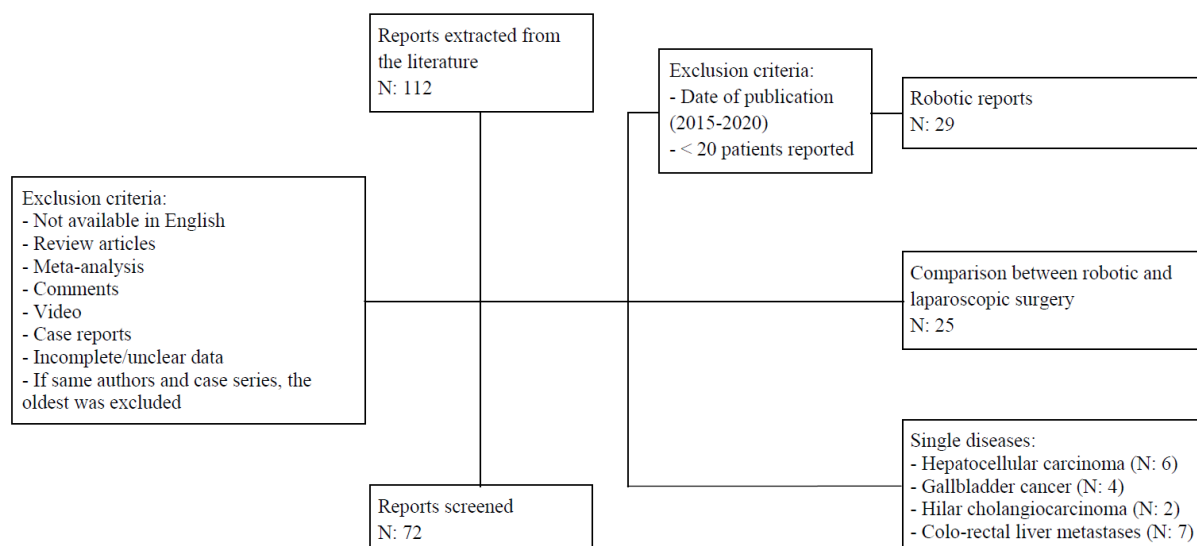


Figure 1. Selection of articles

conversion rate), histopathology (nature of the lesion, median tumor size, number of lesions, margin status, lymphadenectomy), short-term outcomes (overall morbidity, major complications, perioperative blood transfusions, admission to intensive care units, length of hospital stay, surgery-related readmission, reoperation within 30 days, 30- and 90-days mortality), long-term outcomes (disease free survival, overall survival), costs [Figure 1].

Minor and major resections were defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections^[9]. The Clavien-Dindo Classification of surgical complications was adopted to define major complications as grade three or more^[10]. Firstly, 29 publications on robotic liver surgery were selected and reviewed, excluding those reporting less than 20 patients. Secondly, 25 articles comparing robotic and laparoscopic liver resections were reviewed. Eventually, 4 sub-group analyses were conducted including studies on single malignant hepatobiliary diseases: hepatocellular carcinoma (HCC), gallbladder cancer (GBC), hilar cholangiocarcinoma (hCCC), colorectal liver metastases (CRLM).

RESULTS

Robotic liver surgery

Twenty-nine articles, published in the last five years (2015-2020) including a number of patients greater than or equal to 20, were analyzed [Table 1]. The total number of patients reported in 29 studies was 1831, with a median number of 61 patients (range 20-183). The median age was 61 years old (range 45-69.4). All the studies were retrospective and most of them reported cumulative results, without any differentiation between benign and malignant diseases or minor and major liver resections.

Type of liver resection

Referring to the type of resections, 1328 (69.5%) were minor, and 584 (30.5%) were major resections. The number of “technically major resections”^[8] (segments 1, 4a, 7, 8) collected was 214 (11.7%). The studies including resections of these segments reported a longer operative time and greater estimated blood loss (EBL). Nota *et al.*^[11] published a multi-institutional propensity score study (31 matchings), demonstrating that minor robotic resections of postero-superior segments were safe and feasible, improving outcomes in comparison with open surgery [median EBL 180 mL vs. 300 mL, operative time 198 min vs. 255 min, length of stay (LOS) 4 days vs. 10 days].

Table 1. Robotic liver surgery

Authors	Cases	Age	Location	Major/minor	EBL	Time	Conversion	Malignant	RO	LoS	Overall/Major complications
Chong et al. ^[1]	91	58.7	LS, Sg1	19/72	274.6*	259.3*	7.7	100	98.9	4.8	9.9/3.3
Montalti et al. ^[2]	36	62	PS	0/36	415*	306*	13.9	69.4	89	6*	19.4/11.1
Marino et al. ^[4]	40	69.4	LS	18/22	260	305	2.5	100	100	7.4	20/12.5
Pesi et al. ^[5]	51	63	LS, PS	13/38	100	300	2	100	100	5	18/9.8
Magistri et al. ^[6]	22	60.8	LS	2/20	400	318*	0	100	95.5	5.1	68.2/9
Nota et al. ^[11]	51	59	PS	0/51	180	198	8	88.2	84	4	-/6
Daskalaki et al. ^[12]	67	52.5	LS	29/39	438*	293.4*	8.8	55.8	-	6.8*	22/4.4
Hu et al. ^[13]	58	52.2	LS	0/58	80.1*	107*	0	62	100	4.3	1.7/-
Lee et al. ^[14]	70	58	LS	14/56	100	251.5	5.7	74.2	98.2	5	11.4/-
Felli et al. ^[15]	20	64.6	LS, PS	2/18	50	141.5*	0	85	-	-	-
Lai et al. ^[16]	95	62.1	LS, PS	27/75	334.6*	207.4	4	100	96	7.3*	14/1
Li et al. ^[17]	48	62.4	LS, Sg1	48/0	150	276	-	100	72.9	9	58.3/10.4
Guerra et al. ^[18]	59	64	LS, PS	4/78	200	210	12	100	92	6.7	27/5
Goel et al. ^[19]	27	54	LS	0/27	200	295	14.8	100	100	4	3.7/3.7
Khan et al. ^[20]	61	66	LS	8/53	100	240	11.5	100	85.2	5	37.7/11.4
Efanov et al. ^[21]	40	45	PS	2/49	465*	407	0	28	-	11	20/-
Choi et al. ^[22]	69	53	LS	64/16	170	491	9.1	76.8	100	8	43.5/10.6
Sham et al. ^[23]	71	54.8	LS, Sg1	17/54	495*	284*	5.7	98.6	-	3.9*	14.3/4.3
Fruscione et al. ^[24]	57	58.1	LS	57/0	250	194	-	64.9	91.9	4	28.1/25.1
Lim et al. ^[25]	61	66	LS, PS	9/52	-	277	0	100	89	9	25/2
Beard et al. ^[26]	115	61	LS, PS	17/98	-	272*	5.2	93.9	73.7	5	31.3/10.4
Quijano et al. ^[27]	21	59.3	LS, PS	4/17	-	262*	4.75	65	-	12*	19/4.7
Chen et al. ^[28]	183	60.8	LS, PS	92/91	249	361	1.6	67.2	-	7.5	4.4/2.1
Kingham et al. ^[29]	64	64	LS	6/65	100	163	6.3	78.2	-	-	10.9/4.4
Sucandy et al. ^[30]	75	64	LS	25/50	125	227	0	81	-	3	11/-
Wang et al. ^[31]	92	54.1	LS	92/0	243*	195.5*	1	66.3	-	7.4*	13/1.1
Melstrom et al. ^[32]	97	62	LS, PS	13/84	144*	197*	9.7	85.5	-	-	9.7/-
Ceccarelli et al. ^[33]	70	67	LS, PS	2/89	25	115*	10	70	94.3	3	10.1/1.4
Guadagni et al. ^[34]	20	66	LS	0/20	250*	198.5*	0	20	100	4.7	25/0

Cases: number of patients. Lesions' location: PS: postero-superior segments; LS: laparoscopic segments different from the postero-superiors; LLS: left-lateral sectionectomy. Major/minor resections: number of major/minor, according to the description of the authors or calculated from the data supplied. EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. Malignant: percentage of malignant lesions. RO: percentage of negative margin status. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. "-": not reported

Surgery related factors

Among the 29 studies collected, the median value of EBL was 200 mL (range 25-495) and the median operative time was 260.65 min (range 107-491). Chong et al.^[1] reported results of resections differentiated by difficulty scoring system (DSS). The authors confirmed a correlation between DSS and EBL and operative time. The mean EBL was 274.6 mL (146.4 mL for low difficulty resections and 646.7 mL for high difficulty resections), while the mean operative time was 259.3 min (205.9 min for low difficulty resections and 433.1 min for high difficulty resections)^[35]. Daskalaki et al.^[12] indicated the specific results of major and minor resections, showing higher EBL and conversion rate, longer operative time and LOS for major resections: mean EBL 354.7 mL vs. 570 mL, mean operative time 223.2 min vs. 404 min, conversion rate 2.5% vs. 17.2%, mean LOS 5.2 days vs. 8.8 days.

Only 10 articles reported data about the use of the Pringle maneuver and the median rate of its application was 23.6% (range 0-55.6). The agreement in the literature on this topic is limited and some authors considered pedicle clamping unnecessary in most cases during RS^[13-15,36]. Otherwise, other authors preferred a routine use of pedicle clamping during major hepatectomies or for difficult resections^[2,16-18].

Conversion to open surgery occurred with a median of 5.45% (range 0-14.8). Four authors reported that higher conversions rates (greater than 10%) were related to bleeding, adhesions, technical difficulty, advanced oncological diseases and the requirement of adequate oncologic margins^[2,18-20].

Histopathology

Among the indications for RS of the 29 articles reviewed, malignancies were the 84% of the cases, in particular the most frequent indication was HCC (40%), followed by CRLM (21%), other metastases (14%), cholangiocarcinoma (CCC) (9%), GBC (3%) and other malignancies (13%). The median tumor size was 33 mm (range 17.8-73). Efanov *et al.*^[21] emphasized that resections of greater tumors (up to 73 mm) should be performed by RS at the end of the surgeon's learning process. The median rate of R0 margin status was 95.5% (range 72.9-100).

Interestingly, Khan *et al.*^[20] published an international multicenter study, in which they stratified their results for RS by tumor type (3-years overall survival was 90% for HCC, 65% for GBC and 49% for CCC) and reached comparable long-term outcomes, such as overall survival (OS) and disease free survival (DFS), to those of open and laparoscopic liver resections available in literature.

In conclusion, despite the lack of long-term results available in literature, RS is considered feasible and effective in the treatment of malignant diseases.

Short-term postoperative outcomes

ICU admission rate was described in 6 studies reporting a median frequency of 27.9% of patients requiring ICU postoperative care (range 0-83.8). Daskalaki *et al.*^[12], even if reporting the 83.8% of ICU admission after RS, described a reduction in the length of the ICU stay in comparison with open surgery (2.1 days vs. 3.3 days, respectively).

The median rate of overall complications of the 29 reports reviewed was 18.5% (range 1.7-68.2), with a median rate of major complications (Clavien-Dindo grade 3 or greater) of 4.7% (range 0-25). Choi *et al.*^[22] reported a greater frequency of overall and major complications in minor resections compared to major hepatectomies (46.7% vs. 42.6% and 13.3% vs. 9.3%, respectively), otherwise Daskalaki *et al.*^[12] described a major rate of overall and major complications in major resections (31% vs. 15.3% and 6.8% vs. 2.5%, respectively).

The median LOS was 5.05 days (range 3-12). In particular, 16 studies reporting an operative time longer than 250 min revealed greater LOS, overall and major complications. Among these 16 articles, the median operative time was 294.2 min (range 251.5-491) and the corresponding median LOS was 6.4 days (range 3.9-12), overall complications rate was 9% (range 1-36) and major complications rate was 3.5 % (range 1-12).

Hospital costs for RS

Many studies documented the costs of robotic liver resections, which were higher than laparoscopy, but lower than open surgery. Daskalaki *et al.*^[12] published a retrospective single center comparative study between robotic and open liver surgery, describing higher average costs for open surgery (\$37,518 vs. \$41,948) including readmissions costs, mainly because of the significant impact of ICU stay, inpatient nursing, and pharmacy costs. Similarly, Sham *et al.*^[23] revealed higher perioperative costs, but significantly lower postoperative and total hospital direct costs for RS (\$14,754 vs. \$18,998), encouraging the development of RS.

Table 2. Robotic vs. laparoscopic liver resections

Authors	Cases		Location		Major/minor		EBL		Time		Conversion		LoS		Overall/major complications	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Chong <i>et al.</i> ^[1]	91	92	LS, Sg1	LS, Sg1	19/72	4/88	275*	212*	259* [#]	217* [#]	7.7	12	4.8	4.9	9.8/3.3	5.4/0
Montalti <i>et al.</i> ^[2]	36	72	PS	PS	0/36	0/72	415*	437*	306*	295*	14	9.7	6*	4.9*	19.4/11.1	19.4/6.9
Magistri <i>et al.</i> ^[6]	22	24	LS, PS	LS, PS	2/20	0/24	400	328	318* [#]	211* [#]	0 [#]	16.7 [#]	5.1	6.2	68.1/9	100/12.5
Hu <i>et al.</i> ^[13]	58	54	LLS	LLS	0/58	0/54	80*	109*	107*	96*	0	1.9	4.3	4.4	1.7/-	3.7/-
Lee <i>et al.</i> ^[14]	70	66	LS	LS	14/70	2/66	100	100	251 [#]	215 [#]	5.7	12.1	5	5	11.4/-	4.5/-
Lai <i>et al.</i> ^[16]	95	35	LS, PS	LS	27/75	1/34	335	336	207* [#]	134* [#]	4	5.7	7.3*	7.1*	14.7/1	20/-
Efanov <i>et al.</i> ^[21]	40	91	LS, PS	LS, PS	2/40	11/91	465	302	407 [#]	296 [#]	0	0	11 [#]	9 [#]	20/-	16.4/-
Fruscione <i>et al.</i> ^[24]	57	116	LS	LS	57/0	116/0	250	400	194	204	-	-	4	5	28/7	35.3/9.4
Lim <i>et al.</i> ^[25]	55	55	LS, PS	LS, PS	4/51	8/47	-	-	254	257	0	0	9	7	21.8/1.8	12.7/0
Beard <i>et al.</i> ^[26]	115	115	LS, PS	LS, PS	97/18	94/21	-	-	272*	253*	5.2 [#]	12 [#]	5	4	31.3/10.4	27.8/14.7
Wang <i>et al.</i> ^[31]	92	48	LS	LS	92/0	48/0	243* [#]	346* [#]	195*	199*	1 [#]	10.4 [#]	7.4*	7*	13/1	10.4/0
Spampinato <i>et al.</i> ^[36]	25	25	LS	LS	25/0	25/0	250	400	430	360	4	4	8	7	16/4	48/12
Kim <i>et al.</i> ^[37]	12	31	LLS	LLS	0/12	0/31	225	150	404 [#]	246 [#]	-	1	7	7	-/16.6	-/9.6
Packiam <i>et al.</i> ^[38]	11	18	LLS	LLS	0/11	0/18	30	30	175	188	0	0	4 [#]	3 [#]	27.2/0	0
Salloum <i>et al.</i> ^[39]	14	14	LLS	LLS	0/14	0/14	265*	121*	203* [#]	140* [#]	14	0	6*	6*	7.1/0	7.1/21.4
Croner <i>et al.</i> ^[40]	10	19	LS	LS	0/10	-	306	356	321	242	-	-	7	8	10/0	15.7/5.2
Ji <i>et al.</i> ^[41]	13	20	LS, Sg1	LS	9/4	4/16	280	350	338	130	0	10	6.7	5.2	7.7/-	10/-
Wu <i>et al.</i> ^[42]	52	69	LS	LS	20/52	10/69	325 ^{o,*#}	173 ^{o,*#}	380 ^{o,*#}	227 ^{o,*#}	5 ^o	12 ^o	7.9 ^o	7.2 ^o	5.7/0 ^o	5.7/- ^o
Troisi <i>et al.</i> ^[43]	40	223	LS, PS	LS, PS	0/40	82/223	330 [#]	174 [#]	271	262	20	7.6	6.1	5.9	12.5/10	12.5/8.9
Tsung <i>et al.</i> ^[44]	57	114	LS	LS	21/36	42/72	200	100	253 [#]	198 [#]	7	8.8	4	4	19.2/1.7	25.4/0.8
Tranchart <i>et al.</i> ^[45]	28	28	LS, PS	LS, PS	0/28	0/28	200	150	210 [#]	176 [#]	14	7.1	6	5.5	17.8/10.7	17.8/10.7
Berber <i>et al.</i> ^[46]	9	23	LLS	LLS	0/9	0/12	136*	155*	258*	234*	1	0	-	-	11/-	17/-
Yu <i>et al.</i> ^[47]	13	17	LS	LS	3/10	11/6	388	343	291	241	0	0	7.8*	9.5*	0	11.7/-
Zeng <i>et al.</i> ^[48]	3	5	LS	LS	0/3	0/5	316*	290*	370*	249*	0	20	3	5	-	-
Lin <i>et al.</i> ^[49]	25	11	LS	LS	3/25	2/11	271	295	319	315	-	-	7.5	7	24/-	27.2/-

In case of PSM, only its data were reported. R: robotic surgery; L: laparoscopic surgery. °: referred to the sub-group of HCC. Cases: number of patients. Lesions location: PS:postero-superior segments; LS: laparoscopic segments different from the postero-superiors; LLS: left-lateral sectionectomy. Major/minor resections: number of major/minor, according to the description of the authors or calculated from the data supplied. EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. Statistically significant results (P -value < 0.05) are expressed “*”, if reported in the articles. “-”: not reported

Robotic vs. laparoscopic liver surgery

Twenty-five comparative studies between robotic and laparoscopic liver surgery, including 1,043 cases (range 3-115) and 1,385 cases (range 5-223) respectively, were reviewed [Table 2]. These reports were published from 2010 to 2020. All of them were retrospective and 5 were propensity score matching studies (PSM). In case of PSM only results of the matchings were considered.

Left lateral sectionectomy

Left lateral sectionectomy (LLS) is currently performed with laparoscopy as a standard of care. Five studies focused on robotic and laparoscopic LLS, including 106 (range 9-58) and 206 (range 18-80) cases, respectively. Most of the articles reported similar perioperative outcomes between laparoscopy and RS. Many authors concluded that laparoscopic LLS remains the gold standard, since RS did not add any significant benefit, but increased the costs^[13,37-39]. However, Hu *et al.*^[13] established that RS could be the best choice to treat complex cases of LLS (tumor size > 10 cm in diameter, proximity of the tumor to major vessels, BMI > 30 kg/m², combined lymphadenectomy or choledochoscopy, huge left lateral section embedded in splenic fossa), reporting significantly lower EBL than in laparoscopy for these cases (131.9 mL vs. 320.8 mL, respectively).

Other types of resection

Among the 25 articles reviewed, the numbers of major and minor robotic resections included were 395 and 694 (63.7% and 36.3%) respectively, while laparoscopic cases were 460 and 1,002 (68.5% and 31.5%), respectively.

Three papers focused on only major hepatectomies (174 robotic vs. 189 laparoscopic cases). Among these, Fruscione *et al.*^[24] revealed that robotic technical advantages could improve surgical outcomes in comparison with laparoscopy, reducing postoperative ICU admissions (43.9% vs. 61.2%) and 90-day readmissions (7% vs. 28.5%), with a similar median complications rate (28.1% vs. 35.3%) and median LOS (4 days vs. 5 days).

Many authors focused on the ability of RS to overcome laparoscopic drawbacks, particularly simplifying hilar and hepatocaval dissection, suturing and anastomosis, precise vessel dissection or advanced sewing. However, the numbers of complex parenchymal sparing resections involving postero-superior segments or caudate lobe were similar for RS and laparoscopy, 112 (10.7%) vs. 235 (16.9%), respectively.

In complex cases many comparative studies demonstrated similar safety, feasibility and postoperative outcomes, but RS was preferred over laparoscopy, especially when several and multiplanar transection lines were necessary, resulting in safe surgical margins and increasing the rate of MIS resections^[2,21,26]. In the future these advantages could encourage the choice of RS in challenging cases, otherwise not feasible by laparoscopy^[40,41].

Surgery related factors

Considering the 25 articles reviewed, the median EBL for RS and laparoscopy were 261 mL vs. 290 mL (range 30-465 vs. 30-457, respectively). Only three studies reported statistically significant differences of this parameter. Wu *et al.*^[42] and Troisi *et al.*^[43] reported greater EBL for RS (325 mL vs. 173 mL and 330 mL vs. 174 mL, respectively), in contrast with Wang *et al.*^[31] (243 mL vs. 346 mL).

Referring to the use of the Pringle maneuver, Montalti *et al.*^[2] reported its significant use during RS compared to in laparoscopy (55.6% vs. 22.2%, respectively) because of the crush technique, leading to a longer inflow occlusion time and greater severity of complications, evaluated by comprehensive complication index (CCI: 34.6% vs. 18.4%). Conversely, Spampinato *et al.*^[36] published a retrospective comparative multi-institutional study, demonstrating that RS allowed for easier management of bleeding during the transection, making the application of the Pringle maneuver less necessary and reporting a significantly higher EBL for laparoscopy compared to RS (400 mL vs. 250 mL, respectively).

The median operative time for RS and laparoscopy was 271 min (range 107-430) and 227 min (range 96-360), respectively. Ten studies reported statistically significant longer duration with RS compared to laparoscopy, with a mean additional time of 68 min (range 34-153)^[1,6,14,16,21,37,39,42,44,45]. Spampinato *et al.*^[36] specified that longer robotic operative time could be related to instrument replacement and docking time, which could be reduced by improving the training of the surgical team.

In 18 articles the median operative time was longer than 250 min for RS and/or laparoscopy. In these studies, although the frequency of minor resections (69.6% vs. 74.3%, respectively), EBL (293 mL vs. 292.5 mL, respectively), LOS (6.7 days vs. 6.2 days, respectively) and overall complications rates (16% vs. 15.7%, respectively) were similar between RS and laparoscopy, the conversion rate (5% vs. 9.25%, respectively) was lower for RS. These results suggest that RS could increase MIS approach also in complex cases requiring longer operative time.

The reported use of hand-port in RS is lower than in laparoscopy. The reason for this observation could be the distance of the first surgeon from the patient and from the operative field that is mainly occupied by the robotic arms. Moreover, the second surgeon at the operative table could not have enough surgical skills to manage unexpected events. This statement could explain also the lower rate of conversion to hybrid robotic procedures in case of unexpected events. However, many studies reported an easier robotic management of adhesions and major intraoperative complications as bleeding than in laparoscopy, that could explain the lower rate of conversion to open surgery for RS.

The median rates of conversion for RS and laparoscopy were 4% vs. 7.35% (both ranges 0-20). Among the 25 comparative articles reviewed, 4 papers reported a statistically significant higher conversion rate for laparoscopy in comparison with RS^[6,26,31], while the other authors did not reach statistically significant results for this variable. Only Troisi *et al.*^[43] found a higher conversion rate for RS compared to laparoscopic surgery (20% vs. 7.6%, $P = 0.034$) but, considering only resections of postero-superior segments, they showed that RS provided a lower conversion rate (20% vs. 35.3%, $P = 0.38$).

Postoperative outcomes

The median rates of overall robotic and laparoscopic complications were 17.7% vs. 37.6% (ranges 5.7-68.1 vs. 27.2-48), respectively. The median rates of major complications were 2.5% vs. 8.9% (ranges 0-16.6 vs. 0-21.4), respectively.

The median LOS for RS and laparoscopy were 6 days vs. 5.95 days (ranges 3-11 vs. 3-9.5). Only Efanov *et al.*^[21] and Packiam *et al.*^[38] reported a statistically significant longer hospital stay for RS, mainly caused by postoperative complications and ICU stay.

Comparison of costs

Many authors confirmed the major costs of robotic resections, although the annual service fees could be cushioned by the utilization of the robot in other surgical specialties at the same institution. Kim *et al.*^[37] observed that robotic LLS showed higher costs (\$8,183 vs. \$5,190) and longer operative time. Salloum *et al.*^[39] suggested that robotic LLS did not add additional advantages in comparison with laparoscopic outcomes. Furthermore, while perioperative costs were higher in the robotic group, total costs were similar in comparison with laparoscopy (€5,522 vs. €6,035). Berber *et al.*^[46] calculated a general addition of \$500 per case for the robotic equipment. Ji *et al.*^[41] considered RS not routinely applicable, since its higher costs in comparison with laparoscopy (\$12,046 vs. \$7,618). Packiam *et al.*^[38] performed a cost analysis differentiating direct and indirect costs of RS. Only robotic indirect costs were significantly higher, adding \$1,423 per case (\$6,553 vs. \$4,408). However, Yu *et al.*^[47] concluded that RS could really increase in near future, overcoming the drawbacks represented by the major costs (\$11,475 vs. \$6,762) and the absence of transection tools equivalent to those available in laparoscopy.

Robotic surgery in specific malignant diseases

The majority of the publications in the literature report cumulative results, without differentiation between benign and malignant diseases. However, in future probably more specific analyses of RS outcomes for each of the most relevant hepatobiliary malignancies could help in the definition of the standard of care for each one.

Hepatocellular carcinoma

Robotic resections for HCC are feasible, safe, and demonstrated adequate oncologic outcomes. Six retrospective papers, including 294 patients, analyzed the results of RS for HCC [Table 3].

In this field the superiority of robotic MIS over open surgery was confirmed by Chen *et al.*^[28] by a PSM study. Even in challenging major resections, robotic approach showed longer operative time, but shorter

Table 3. Robotic surgery for hepatocellular carcinoma

Authors	Cases	Age	Location	Major/minor	EBL	Time	Conversion	Cirrhosis	RO	LoS	Overall/major complications	DFS/OS
Magistri <i>et al.</i> ^[6]	22	60.8	LS, PS	2/20	400	318*	0	68	95	5.1	68/9	-
Lai <i>et al.</i> ^[16]	95	62.1	LS, PS	27/75	335	207	4	84	96	7.3*	14/1	5-year: 42/65
Lim <i>et al.</i> ^[25]	42	-	-	-	-	-	0	-	97	-	-	3-year: 64/98
Chen <i>et al.</i> ^[28]	81	-	-	34/47	282	343	-	46	97	7.5	5/0	3-year: 72/93
Wu <i>et al.</i> ^[42]	38	60.9	LS	-	-	380	5	-	-	7.9	8/-	-
Han <i>et al.</i> ^[50]	16	54.5	LS	10/16	389	285	0	53	100	8.4	-	-

Cases: number of patients. Lesions' location: PS: postero-superior segments; LS: laparoscopic segments different from the postero-superiors. OS: overall survival; DFS: disease free survival. Major/minor resections: number of major/minor, according to the description of the authors or calculated from the data supplied. EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. RO: percentage of negative margin status. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. DFS and OS: percentage at 3-/5-year. "-": not reported

LOS, improved patients' pain control, not compromising oncologic outcomes and reaching comparable 3-years DFS (72.2% *vs.* 58.0%) and 3-years OS (92.6% *vs.* 93.7%). Magistri *et al.*^[6] and Lai *et al.*^[16] reported less minor robotic postoperative complications, such as pleural effusion, thanks to gentler manipulation of the diaphragm, especially in the case of lesions located in postero-superior segments. In addition, RS allowed lower rates of conversion, a greater number of resections involving the postero-superior segments, and resections of slightly larger tumors, that could explain the higher rate of major hepatectomies. Lai *et al.*^[16] did not find significant differences between robotic and laparoscopic oncologic outcomes (5-years OS: 65% *vs.* 48%, respectively), morbidity and mortality. The authors concluded that robotic MIS was a valid alternative treatment for HCC in selected patients and in the hands of surgeons expert in laparoscopic and robotic liver surgery, following the principles of open liver surgery.

Likewise, Han *et al.*^[50] revealed the safety and feasibility of the robotic approach to complex procedures and anatomical liver resections, and thus the superiority of minimally invasive liver surgery in terms of EBL, complication rate, LOS and risk of ascites, maintaining DFS and OS similar to open surgery.

Gallbladder cancer

RS seems particularly advantageous in the treatment of GBC, overcoming the difficulties related to the laparoscopic approach. Focusing on this field, 4 articles including 51 patients were reviewed [Table 4]. Zeng *et al.*^[48] demonstrated safety and feasibility of both robotic and laparoscopic surgery. Otherwise, Goel *et al.*^[19] and Byun *et al.*^[51] compared results of robotic and open radical cholecystectomy. They achieved similar results between the two approaches, reaching no significant differences in operative time, EBL and number of retrieved lymph nodes, with a reduction of LOS. Likewise, Shen *et al.*^[52] confirmed the feasibility of a complete robotic lymphadenectomy of the hepatic artery, the celiac axis, the hepatoduodenal ligament and retropancreatic nodes, in contrast with laparoscopy. In addition, robotic approach could reduce the risk of major iatrogenic injuries and major bleeding could be more easily managed^[51,52].

In conclusion, in selected cases RS for GBC is considered safe, feasible and effective, even during the initial learning curve, allowing sufficient lymph node dissection and enhancing recovery^[19,51,52].

Hilar cholangiocarcinoma

Even if the advantages of the robotic technique for procedures that require extreme precision and microanastomosis are clear, the scientific literature is lacking in reports about robotic treatment of this disease. Probably further implementation in surgeon expertise and robotic tools are necessary to reach encouraging results that could increase its use. Two articles were selected and their data tabulated [Table 5].

Li *et al.*^[17] highlighted the feasibility of 48 robotic resections for Bismuth-Corlette type I, II or III hilar cholangiocarcinoma. The authors considered RS a valid alternative to open surgery in selected cases,

Table 4. Robotic surgery for gallbladder cancer

Authors	Cases	Age	EBL	Time	Conversion	Lymph nodes	Extension	RO	LoS	Overall/major complications
Goel <i>et al.</i> ^[19]	27	54	200	295	14.8	10/-	pT2-3	100	4	3.7/3.7
Zeng <i>et al.</i> ^[48]	3	-	316*	370*	0	6.3/-	pT2-3	-	3	-
Byun <i>et al.</i> ^[51]	16	64.3	295	198.3*	-	7.2/3	-	100	7	6.3/6.3
Shen <i>et al.</i> ^[52]	5	57.4	210*	200*	0	9/1,3	-	-	7.4*	0

Cases: number of patients. Major/minor resections: number of major/minor, according to the description of the authors or calculated from the data supplied. EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. Lymph nodes: mean number of nodes obtained/mean number of positive nodes. RO: percentage of negative margin status. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. "-": not reported

Table 5. Robotic surgery for hilar cholangiocarcinoma

Authors	Cases	Age	Pre-op. procedures	Type of resection	EBL	Operative time	Conversion	RO	LoS	Overall/major complications	Biliary leak
Li <i>et al.</i> ^[17]	48	62.4	PTBD 41.7	RH/LH + Sg1	150	276	-	72.9	9	58.3/10.4	4.2
Xu <i>et al.</i> ^[53]	10	54	PVE 10, PTBD 60	LH/RH + Sg1 (9) ERH (1)	1360	703	0	-	16	90/30	40

Cases: number of patients. PTBD: percentage of percutaneous trans-hepatic biliary drainage; PVE: percentage of portal vein embolization; RH/LH: right/left hepatectomy; ERH: number of extended right hepatectomies; EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. RO: percentage of negative margin status. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. Biliary leak: percentage. "-": not reported

allowing lymphadenectomy of groups 7, 8, 9, 12 and 13. However, they did not report details about the extension of hepatectomies for each tumor stage and the rates of conversion to open surgery. Conversely, Xu *et al.*^[53] evaluated their results for 10 patients of fully robotic-assisted radical resection for hCCC. The authors demonstrated that this procedure is technically achievable in selected patients by expert surgeons, but without superior results to open surgery. In fact, they observed technical limitations in robotic liver mobilization and exposure, longer operative time and massive EBL, consequently increased morbidity, higher costs and poor long-term outcomes with greater rate of peritoneum implantation and multisite metastases.

Colorectal liver metastases

Many hepatobiliary surgeons encouraged the robotic approach to CRLM, achieving good surgical and oncological outcomes. Seven articles were reviewed, including 242 patients [Table 6]. Beard *et al.*^[26] focused their PSM on RS for CRLM and considered it feasible and safe, being perioperative and long-term oncologic outcomes largely comparable to laparoscopy.

Araujo *et al.*^[54] and Troisi *et al.*^[43] demonstrated feasibility of non-anatomical robotic resections of lesions located in postero-superior segments, simplifying parenchymal sparing resections, not affecting the oncologic outcomes, reducing the necessity of major hepatectomies and overcoming laparoscopic drawbacks.

Fifty-four simultaneous resections of the primary tumor and liver metastases were included. In these cases, RS added additional safety and effectiveness in the management of multiple metastases, improving short-term outcomes such as EBL, bowel function return time and LOS, with the exception of operative time, reaching excellent R0 resection rates^[34,55]. Even in selected cases requiring major liver resections, robotic surgery gained acceptable morbidity^[56]. In addition, it is worth considering that robotic total mesorectal excision demonstrated better preservation of urinary and sexual functions, low conversion rates and favorable morbidity^[49].

Table 6. Robotic surgery for colorectal liver metastases

First Author	Cases	Age	Location	Major/minor	Simultaneous	EBL	Time	Conversion	R0	LoS	Overall/major complications	DFS/OS
Guerra et al. ^[18]	59	64	LS, PS	4/78	4	200	210	12	92	6.7	27/5	3-year: 41.9/66.1
Beard et al. ^[26]	115	61	LS, PS	97/18	-	-	272*	5.2	73.7	5	31.3/10.4	5-year: 38/61
Guadagni et al. ^[34]	20	66	LS	0/20	3	250*	198*	0	100	4.7	25/0	3-year: 35.8/-
Lin et al. ^[49]	25	58.5	LS	3/22	25	271	319	-	100	7.5	24/-	-
Araujo et al. ^[54]	5	59	PS	0/5	-	160*	294*	0	100	4	20/0	-
Dwyer et al. ^[55]	6	59.3	-	0/6	6	316	401	0	100	4.5	33.3/-	-
Navarro et al. ^[56]	12	59	LS, Sg1	4/8	16	274	449	0	100	12	41/16.6	-

Cases: number of patients. Lesions' location: PS: postero-superior segments; LS: laparoscopic segments different from the postero-superiors. Major/minor resections: number of major/minor, according to the description of the Authors or calculated from the data supplied. Simultaneous: resection of the primary and secondary tumors simultaneously. EBL: milliliters (median/*mean). Operative time: minutes (median/*mean). Conversion rate: percentage of procedures converted to open surgery. R0: percentage of negative margin status. LoS: days (median/*mean). Overall/major complications: percentage of all complications/major complications. DFS and OS: percentage at 3-/5-year. "-": not reported

In conclusion, these outcomes could support the use of RS, despite the high operative time and costs.

CONCLUSION

In the field of hepatobiliary surgery, use of the robotic approach is promising, but not standardized yet. International and multicenter studies are limited, only few publications reported long-term outcomes and no randomized trials are available in literature. In the current literature many authors attempted to reach definitive conclusions about the use of RS publishing many reviews/meta-analyses. In general, almost all of these studies found RS as safe and effective with acceptable morbidity in the treatment of liver malignancies as for laparoscopy^[7,57-59]. Furthermore many authors agreed with the necessity of specific training in RS, the high costs and the usefulness of RS in complex cases, such as cirrhotic patients and in complex surgical procedures including microsuturing, biliary dissection, and bilio-enteric anastomosis^[59,60]. However many results of RS are still discordant, mainly in short-term outcomes, and no studies reported definitive indications and contraindications of RS because of the lack of randomized control trials. The comparison among open, laparoscopic, and robotic liver resections demonstrated that the robotic approach achieved similar results to other MIS techniques, enhancing patients' recovery after surgery.

The majority of the studies reported single center initial experiences and considered the robotic learning curve shorter than the laparoscopic one, especially for surgeons with advanced skills in open liver surgery^[21,22,29,33]. Efanov et al.^[21] established that 8-10 robotic procedures can be adequate to significantly increase the surgeons' experience and the ability to perform difficult procedures.

Choi et al.^[22] reported results from single center and single surgeon's activity, emphasizing the usefulness of high experience on open liver surgery to approach the robotic resections, making safe and feasible all types of anatomic liver resections, even more complex ones, such as staged hepatectomy and living donor right hepatectomy. Ceccarelli et al.^[33], describing their robotic learning curve program organized in a network between high and low volume centers, demonstrated that this strategy provides a proper standard of care without the need of reaching referral centers for the patients, even in particularly complex cases. In addition, this protocol can improve surgical skills, shortening the learning curve.

Interestingly, Lai et al.^[61] reviewed the learning curves of robotic and laparoscopic hepatectomy and concluded that a qualified robotic surgeon should have great knowledge of liver anatomy, enough experience in open liver surgery and in the management of its major complications and a good training in both laparoscopic and robotic surgery.

In conclusion, in the era of MIS in which surgical innovations are increasing, even if the younger surgeons are more confident with MIS, both open and laparoscopic surgical experiences are necessary in order to shorten the learning curve of robotic liver surgery and all the surgeons should receive specific training for RS.

Even though robotic liver surgery allows attainment of excellent oncologic results with adequate Ro margins, long-term outcomes are still lacking, probably because of the recent introduction of this technique.

Regarding the type of liver resection, robotic LLS is considered inappropriate in comparison with the laparoscopic one, which is actually the standard of care. In fact, while perioperative outcomes are similar, costs are markedly higher for RS. On the contrary, complex cases could take advantages from RS, thus increasing the rate of MIS.

Even for other type of resections, the results available in the current literature encourage the use of robotic surgery in complex cases, for example for lesions located in postero-superior segments. Furthermore, many studies reported easier management of major intraoperative complications, such as bleeding, that could explain the lower rate of conversion compared with laparoscopy.

Among the comparative studies between MIS techniques, many of them reported a greater number of major resections for robotic surgery. Some authors explained these results with the reduced difficulty of robotic major hepatectomies in comparison with laparoscopy, allowing a potential increase of MIS in more complex cases^[24,40,41].

One of the most relevant drawbacks of robotic surgery remain higher costs. Almost all the comparative studies confirmed robotic perioperative higher costs with reduced postoperative ones^[23]. Even for this reason, many authors encouraged the use of RS only in complex cases.

It is possible that the increasing spread of robotic surgery and the introduction of new robotic platforms with industry competition could lead to a consistent reduction of these costs.

Regarding the application of the robotic approach in specific diseases, RS for HCC and liver metastases achieved good results, allowing parenchymal sparing resections, even in difficult locations.

Furthermore, the robotic approach to biliary tumors seems to be the most promising application of robotic surgery, because of the need for extensive lymph node dissection and of bilio-enteric anastomoses. Currently, there are discordant opinions regarding hCCC, whereas robotic surgery for GBC can add relevant benefits, increasing the rate of MIS without compromising oncologic results.

In conclusion, different techniques should be tailored to each patient, applying MIS when possible, particularly in cirrhotic patients and in the context of liver transplantation^[15,34]. Thus, in a modern hepatobiliary center, both open surgery and MIS should be provided, including the robotic technique, in order to safely deal with different liver diseases requiring complex procedures^[6].

In the future the technological innovation could lead to more complete, less expensive and smaller robotic systems with additional devices or software for RS, that could really change the actual scenario of MIS overcoming many of the drawbacks of RS. For example, it could become possible to approach the operation without the second surgeon, the equipment could be smaller, the docking could be easier and quicker and costs reduced thanks to the market competition.

Although a lot of hepatobiliary centers worldwide are already experienced in robotic liver surgery, more and larger studies are necessary to define its real benefits compared with laparoscopy, in order to standardize patient selection criteria and its use.

DECLARATIONS

Authors' contributions

Designed and performed the research: Ruzzenente A, Alaimo L

Collected the data: Conci S, Bagante F

Analyzed the data: Campagnaro T, Pedrazzani C

Supervised the work: Ruzzenente A, Guglielmi A

Wrote and finally approved the manuscript: Ruzzenente A, Alaimo L, Conci S, Bagante F, Campagnaro T, Pedrazzani C, Guglielmi A

Availability of data and materials

A search of the current literature on robotic liver surgery was conducted in PubMed, Medline, PMC and Google Scholar databases.

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None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figures should be cited in numeric order (e.g., Figure 1, Figure 2) and placed after the paragraph where it is first cited;

Figures can be submitted in format of tiff, psd, AI or jpeg, with resolution of 300-600 dpi;

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Tables should be provided in editable form like DOC or DOCX format (picture is not allowed);

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Abbreviations should be defined upon first appearance in the abstract, main text, and in figure or table captions and used consistently thereafter. Non-standard abbreviations are not allowed unless they appear at least three times in the text. Commonly-used abbreviations, such as DNA, RNA, ATP, *etc.*, can be used directly without definition. Abbreviations in titles and keywords should be avoided, except for the ones which are widely used.

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General italic words like *vs.*, *et al.*, *etc.*, *in vivo*, *in vitro*; *t* test, *F* test, *U* test; related coefficient as *r*, sample number as *n*, and probability as *P*; names of genes; names of bacteria and biology species in Latin.

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Numbers appearing at the beginning of sentences should be expressed in English. When there are two or more numbers in a paragraph, they should be expressed as Arabic numerals; when there is only one number in a paragraph, number < 10 should be expressed in English and number > 10 should be expressed as Arabic numerals. 12345678 should be written as 12,345,678.

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Equations should be editable and not appear in a picture format. Authors are advised to use either the Microsoft Equation Editor or the MathType for display and inline equations.

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8.1. Initial check

8.1.1. Initial manuscript check

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