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Review

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Conventional and robotic transanal minimally invasive surgery for rectal neoplasia

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Abstract

The treatment of rectal cancer is evolving at a rapid pace in parallel with advancements in surgical technique. One such advancement is the application of the laparoscopic platform to the transanal approach, coined transanal minimally invasive surgery (TAMIS). TAMIS overcomes many of the shortcomings of the traditional transanal approach to the local resection of rectal neoplasia, offering greater visualization and access to the middle and upper rectum with improved oncologic outcomes. Following the introduction of conventional TAMIS, the robotic platform was introduced and applied in analogous fashion. Over the past decade, data have accumulated enabling the comparison of the two approaches most notably with regard to patient morbidity, mortality, and oncologic outcomes. This review discusses the most recently available outcomes regarding conventional and robotic TAMIS and provides a comparison of the two platforms in the treatment of rectal neoplasia. While randomized controlled trials comparing the two platforms are lacking, important differences have been identified. Conventional TAMIS is the more cost-effective approach while advancements in the robotic platform allow the surgeon to be seated and ergonomically optimized, allowing greater visualization and ease of suturing. Differences in oncologic outcomes between the two platforms have not been identified. Head-to-head randomized controlled trials are required to determine if any differences in functional or oncologic outcomes exist.

Keywords: Rectal cancer, transanal minimally invasive surgery (TAMIS), laparoscopy, robotic surgery



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INTRODUCTION

Our understanding of rectal cancer is advancing at a rapid pace. Treatment options have expanded requiring surgeons to be facile at not only traditional open surgery, but also minimally invasive techniques, such as the laparoscopic and robotic platforms. Minimally invasive surgery techniques have been applied not only to the intra-abdominal approach, but also transanal approach as well. Atallah, Albert and Larach were the first to report this application in their seminal paper describing the approach of single-port laparoscopy, coining the term transanal minimally invasive surgery (TAMIS) in 2009^[1]. TAMIS was established to serve as an alternative to transanal endoscopic microsurgery (TEM). Both TEM and TAMIS demonstrate superior oncological results over traditional transanal excision (TAE)^[2]. While TEM is safe and effective for the treatment of early rectal cancer, its widespread use has been hampered by its high cost of specialized instrumentation and steep learning curve^[3,4]. TAMIS is a technique of single-port laparoscopy enabling the use of widely used laparoscopic instruments with the access of TEM, with reduced cost and possibly less trauma to the anal sphincter^[1,5]. The TEM platform offers improved access to higher lesions with retraction of the rectal valves.

INDICATIONS FOR TAMIS

The indications for TAMIS have traditionally followed the same guidelines as for open transanal excision of rectal tumors set forth by the National Comprehensive Cancer Network (NCCN)^[6]. Tumors should be < 3 cm in size and encompass less than one-third of the circumference of the bowel lumen. However, TAMIS overcomes many of these historical limitations of TAE by offering greater access to middle and upper rectal lesions and improved visualization in a confined operating field. Lesion location is usually < 15 cm from the anal verge and because of the seating of the transanal platform (discussed below), tumors less than 4 cm from the anal verge may require a hybrid approach with traditional TAE. Tumor pathology must be favorable. Thus, benign disease (polyps without submucosal invasion or excisional biopsy for masses of uncertain malignant potential) or uT1 malignant disease with favorable tumor characteristics (no lymphovascular invasion, perineural invasion, or mucinous component) are appropriate^[7,8]. TAMIS also has a role in local excision following incomplete polypectomy to provide negative margins, as well as in cases of palliative resection in patients who are unfit for total mesorectal excision (TME)^[9]. The quality of local excision appears to be equally achieved as that by TEM^[10]. Following excision, if any high-risk features are identified, such as sm3 invasion, lymphovascular invasion, or positive margins, further treatment is recommended^[11]. Notably, no negative effects are seen on oncologic outcomes for subsequent radical resection^[12].

OPERATIVE OVERVIEW

TAMIS is traditionally performed under general anesthesia, but spinal anesthesia has also been described^[13–16]. Advocates for spinal anesthesia have suggested that this modality offers more stable pneumorectum due to improved rectal wall relaxation^[14]. Once the transanal port is inserted and pneumorectum is established, the lesion is identified, and a 0.5–1.0 cm margin is marked circumferentially using electrocautery. Either full thickness or submucosal dissection ensues. Once excised, the specimen is oriented and sent to pathology. Pneumorectum is reestablished under slightly reduced pressure to allow for closure of the defect^[17]. Should there be inadvertent intraperitoneal entry, standard laparoscopic abdominal access can then be established with ports placed to assist with retraction for excision of the specimen as well as closure of the defect^[1,17]. It has also been shown that the defect may be left open, in the absence of peritoneal entry, and it is generally done if a tension-free repair is not deemed possible^[18]. However, if left open, there may be an increased risk of postoperative bleeding^[19,20]. Although an increased risk of infection may also be a concern with an open defect, this has not been conclusively shown^[18–20].

TECHNICAL DETAILS

Patients may be positioned according to surgeon preference. Some prefer to always position patients in high dorsal lithotomy regardless of tumor location ensuring abdominal access, should there be inadvertent peritoneal entry^[1,11,15,21]. Others prefer patients to be positioned to allow the target lesion to be centered at the 6 o'clock position. Thus, patients with anterior tumors are placed in prone jackknife, and patients with posterior tumors are placed in dorsal lithotomy^[17,22,23]. Lateral decubitus position is utilized for lateral tumors^[23]. Split-leg position is necessary to facilitate exposure in lateral decubitus or prone jackknife^[17].

Multiple ports have been described and utilized. Currently, there are two FDA-approved devices. Atallah *et al.*^[1] initially described TAMIS with a single-incision laparoscopic surgery port (SILSTM Port, Covidien, Mansfield, MA), which is lubricated and introduced into the anal canal by steady manual pressure anchoring just above the anorectal ring. Once in place, endoscopic access is gained and pneumorectum is established. The SILS port is made of a soft, flexible thermoplastic elastomer allowing for conformity and provides for three cannulas enabling instrumentation with commonly used laparoscopic instruments. It is 35 mm in diameter and 37 mm in length. The second FDA-approved port is the GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, CA) and is the only disposable multichannel port specifically designed for TAMIS^[7,13,24]. It comes in three access channel sizes: 4 cm × 4 cm, 4 cm × 5.5 cm, and 4 cm × 9 cm. The GelPOINT Path Long Channel is also available and allows reach of lesions up to 15 cm from the anal verge, and for visually obstructed lesions at rectal folds^[17]. Similar to SILS, the GelPOINT Path port is lubricated and seated into the anal canal with steady manual pressure. The SILS port is advantageous for use in patients with narrow or fibrotic anal canals that prohibit the placement of the GelPOINT Path^[17]. In addition to the SILS and GelPOINT Path ports, multiple other transanal ports have been described [Table 1]^[11,13,14,17,18,21,25-29].

CONVENTIONAL TAMIS [TABLE 1]

In the 6 patients included in their initial publication, Atallah *et al.*^[1] described tumor locations ranging from 6 to 11.5 cm from the anal verge, with operative times of 4 patients that were less than 60 min, one patient of 121 min (difficulty maintaining insufflation) and another patient of 192 min (difficult anterior intraperitoneal lesion). Set up times averaged less than 2 min per patient. One patient had positive margins and underwent fulguration. There were no complications through six postoperative weeks, and all patients were discharged by postoperative day two (average 0.83 days).

A systematic review was published in 2014 by Martin-Perez *et al.*^[13] analyzing 33 retrospective studies and case reports and 3 abstracts, amounting to 390 TAMIS procedures for local excision of rectal neoplasia from 16 countries. Of these, 152 (39%) resections were performed for benign disease (adenomas and high-grade dysplasia), 209 (53.5%) for malignancy (carcinoma in situ and invasive disease), and 29 (7.5%) for other pathology. Average size of lesions was 3.1 cm (range 0.8-4.75 cm), mean distance was 7.6 cm (range 3-15 cm) from the anal verge. Twenty-five studies reported on margin positivity, present in 12 of 275 cases (4.36%), and tumor fragmentation occurring in 4.1% of cases. Mean operative time was 76 min (range 25-162 min). Nine of 390 cases required conversion to TAE, TEM or abdominal laparoscopy. Average length of stay was 2 days. Complications occurred in 29 cases (7.4%), with 10 cases of self-limited bleeding and 4 cases of peritoneal entry. Recurrence was described in 16 publications, totaling 259 cases, and occurred in 7 (2.7%) cases at a 7.1-month mean follow-up^[13].

Since these early studies, larger series have been published shedding more light on intermediate outcomes^[11,17,18,21,23,25-27,30]. The largest series to date was published by Lee *et al.*^[11] in 2018, who reported their intermediate outcomes in 200 consecutive resections in 196 patients. Notably, 185 (92%) of cases were performed with laparoscopic instrumentation while 15 (8%) were performed with the da Vinci Si robotic

Table 1. Outcomes of selected cases following laparoscopic TAMIS

Author, Publication	Transanal Port	Patients (n)	Indications (Pathology)	Operative Time (min)	Tumor Distance from AV (cm)	Tumor Size (cm)	Defect Closure	Margins Positive (n)	Length of Stay (days)	Conversions/Complications	Recurrence (n)	Follow Up
Martin-Perez et al. ^[13] , <i>Tech Coloproctol</i> 2014	Multiple	390	152 benign, 209 malignant, 29 others	76	7.6	3.1	-	12 (4 additional fragmented)	1.9	9 conversions, 34 complications	7	7.1 months
Hahnloser et al. ^[18] , <i>Colorectal Dis</i> 2014	SILS	75	42 benign, 32 malignant, 1 carcinoid	median 77 (25-245)	6.4 (± 2.3)	3.9 (± 1.6)	40 (53%) closed, 35 (47%) open	3 (4%)	Median 3.4 (range 1-21)	0 conversions; 7 (9%) Intraop; 15 (19%) Postop	0	median 385 (67-884) days
McLemore et al. ^[17] , <i>Am J Surg</i> 2014	GelPOINT Path, Long Channel, SILS	32	10 benign, 22 malignant	123 (± 62)	4.0 (± 3.0)	3.0 (± 2.0)	32 (100%)	1 (3%)	2.5 (± 2.0)	3 (10%) with lap assistance; 25% morbidity	0	range 3 to 23 months
Schiphorst et al. ^[28] , <i>DCR</i> 2014	SILS	37	23 benign, 13 malignant	median 64 (17-211)	median 7 (0-19) from dentate line	Median 18 cm ²	27 (73%)	6 (16%)	1 (1-23)	1 (3%) conversion; 14% morbidity	1	median 11 (3-19)
Sumrien et al. ^[29] , <i>Anticancer Res</i> 2016	GelPOINT Path or SILS	28	17 benign, 11 malignant	all cases < 60 min	not reported	benign 5 (1.2-11.5); malignant 4.3 (1.2-9.5)	28 (100%)	5 (18%)	1.5	10% conversion; 25% morbidity	1 benign, 1 malignant	3 months
Quaresima et al. ^[25] , <i>JSL</i> 2016	GelPOINT Path or SILS	31	17 benign, 10 malignant, 4 others	not reported	9.5 (6-15)	2.4 (1-5)	31 (100%)	3.2%	Median 3 (2-7)	0% conversion; 9.6% complication	1 benign	30 (1-79) months
Keller et al. ^[21] , <i>J Am Coll Surg</i> 2016	GelPOINT Path or SILS	75	59 benign, 17 malignant	76 (± 36.1)	median 10 (6-16)	3.2 (± 3.1)	69 (92%)	5 (6.7%)	median 1 (0-6)	3 (4%) peritoneal entries w/2 loop ileostomies; 3 (4%) postop	1	median 39.5 (10.5-65.3) months
García-Flores et al. ^[26] , <i>Surg Innov</i> 2017	GelPOINT Path	32	15 benign, 12 malignant, 5 others	69 (35-210)	5.6 ± 1.5	14.5 (± 14.4) cm ²	32 (100%)	1	3.9 (2-26)	22% complication	1 benign, 2 malignant (10.3%)	median 26 months
Chen et al. ^[27] , <i>World J Gastrointest Oncol</i> 2018	SILS	25	3 benign, 22 malignant	61.3 (± 25.5)	8.4 (± 1.6)	1.1 (± 0.5)	25 (100%)	0 benign, 5 malignant (20%)	2.7 (± 1.4)	0% conversion; 0% complications	0	8 weeks
Lee et al. ^[11] , <i>Ann Surg</i> 2018	GelPOINT Path or SILS	200	90 benign, 110 malignant	69.5 (± 37.9)	7.2 (± 3.3)	2.9 (± 1.5)	188 (94%)	14 (7%); 9 (5%) fragmentation	76% POD 0, 28% POD 1, 20% POD 2	4% peritoneal entry, 2% abdominal assistance; 4% intraop, 11% postop	6% (distant in 2%)	14.4 (± 17.4)
Lee et al. ^[4] , <i>Surg Endosc</i> 2019	GelPOINT Path	21	15 benign, 4 malignant, 2 others	100 (± 55)	7.8 (± 2.3)	17 (2.1-55.0) cm ²	100%	2 (9.5%)	median 5 (± 18) hours	1 (5%) peritoneal entry with abdominal assistance	not recorded	not recorded

Mean unless otherwise stated in column header

system (Intuitive Surgical Inc., Sunnyvale, CA). Operations were performed with either the SILS port or GelPOINT Path port. Indications for operation were benign rectal lesions not amenable to endoscopic resection, namely low-grade neuroendocrine tumors ≤ 2 cm in diameter, node-negative cT1 rectal cancer ≤ 3 cm in diameter, well-differentiated, and no lymphovascular invasion present. Palliative indications included patients with more advanced cancer (cT2, cT3) or histologically unfavorable cT1 lesions who were unwilling or unfit to undergo radical excision, and patients who exhibited endoscopic evidence of complete clinical response following neoadjuvant therapy. Final surgical pathology revealed 90 benign lesions and 110 malignant lesions. Notably, 11 of 110 patients with malignant lesions received neoadjuvant therapy. Twenty patients had pT2-3 or ypT2-3 tumors and underwent subsequent radical resection, received adjuvant treatment, or refused further treatment. Mean tumor size was 2.9 ± 1.5 cm, and distance from anal verge was 7.2 cm (range 2-17 cm). Fourteen patients (7%) had positive margins, of which 9 patients had malignant lesions. Eight of these 9 patients with malignancy were pT2 or higher and radical resection was recommended. Ninety-five percent of specimens were submitted without fragmentation. Mean operative time was 69.5 ± 37.9 min. Defects were closed in 188 (94%) cases and were left open due to the inability to obtain a tension-free closure. Peritoneal entry occurred in 8 (4%) cases, of which half were amenable to closure by TAMIS while the other half required abdominal access. Intraoperative complication rate was 8%. Morbidity was 11%, most commonly due to hemorrhage (9%), urinary retention (4%), and scrotal or subcutaneous emphysema (3%). Three patients suffered major morbidity. One patient required a diverting ileostomy for a symptomatic nonhealing rectal wound with fistula formation to the perineum. One patient was readmitted on postoperative day 3 with significant perirectal inflammation which resolved with medical management. One patient developed a rectovaginal fistula after a repeat TAMIS excision of a local recurrence. This resolved with conservative management after two months. Most patients (76%) were discharged following the procedure from the postanesthesia care unit. Mean follow-up for patients with benign and malignant lesions undergoing TAMIS for curative intent was 13.6 ± 17.3 months and 14.4 ± 17.4 months, respectively, with local recurrence rates of 3 and 6%, with distant metastases in 2%. Mean time to recurrence following resection of both benign and malignant lesions was 17 months. Cumulative disease-free survival for patients undergoing resection of benign neoplasms was 98, 94, and 94% and for malignant neoplasms 96, 93, and 84% at 1-, 2-, and 3-year follow-up, respectively.

Keller *et al.*^[21] published their series of 75 consecutive patients undergoing 76 resections. Indications followed NCCN guidelines for TAE, as well as patients unfit or unwilling to undergo radical resection for more advanced pathology. Median lesion distance from anal verge was 10 cm (range 6 to 16 cm). The GelPOINT PATH or SILS port was used for access. Mean operative time was 76 ± 36.1 min. Only 1 lesion was fragmented. Inadvertent peritoneal entry occurred in 3 cases, with 2 of these 3 patients undergoing creation of a protective loop ileostomy to assure healing. Postoperatively, there were 3 complications (4%); one each of bleeding, rectovaginal fistula, and rectal stricture. One case was aborted after intraoperative assessment deemed it unresectable by the transanal approach. Defects were closed in 69 cases, with no complications noted in the 6 cases in which the defect was left open. There were no functional complications noted following resection. Median length of stay was 1 day (range 0-6 days). Fifty-nine resections were performed for benign disease, while 17 resections were performed for malignancy. Of the malignant resections, final pathology yielded 4 pT2 lesions and 1 pT3 lesion, and all of these patients underwent further treatment without apparent oncologic or technical compromise. There were 5 cases of positive margins following resection, 3 of which were pT2 lesions, 1 pT1 lesion and 1 gastrointestinal stromal tumor (GIST). Thus, an important point of emphasis in this study was the high rate of margin positivity in T2 lesions, positive in 3 of 4 cases. Mean follow-up was 36.5 ± 14.8 months. In the 17 malignant cases in the patients who did not undergo immediate radical resection, there was 1 recurrence (5.8%), occurring locally at 9 months after excision. No mortalities were recorded during the study follow-up period.

ROBOTIC TAMIS [TABLE 2]

Following the utilization of standard and advanced laparoscopic tools for transanal surgery came the application of the robotic platform to transanal surgery^[8,23,31-37]. By utilizing the robotic platform, one can take advantage of its three-dimensional imaging and multidegree movement which may be limited in the narrow working space of the rectum. Tasks such as full thickness dissection and closure of rectal wall defects that may otherwise be technically and ergonomically challenging laparoscopically might be more easily performed. Robotic TAMIS allows the working surgeon to be seated and ergonomically optimized, enabling greater ease of suturing^[23]. It has also been suggested that the robotic platform permits better visualization and maneuverability, which may allow for more aggressive resection^[23].

Preclinical cadaveric studies began in 2010 and confirmed the feasibility of applying the da Vinci system and illustrated the possibility of side or parallel approach to docking the da Vinci robotic cart^[38,39]. Hompes *et al.*^[39,40] applied a glove port, which they had previously described for TAMIS, for use with the robot. Creatively designed, the port consisted of a circular anal dilator, a standard wound retractor, and a surgical glove allowing for greater working room which minimized arm collisions^[39,40]. The first human study was published by Atallah *et al.*^[41], which described the resection of a 3-cm tubulovillous adenoma 7 cm from the anal verge in a 58-year-old female. The patient was in modified lithotomy, and the GelPOINT port was utilized, along with three arms of the da Vinci robot via 8-mm trocars placed in the port cannulas. The robot was docked over the patient's right shoulder. The defect was closed with a V-Loc 180 Absorbable Wound Closure Device (Covidien, Mansfield, MA). Operative time was 105 min and there were no complications. Initial publications following these initial experiences were primarily case reports, but since then larger series have been published^[42-44].

Hompes *et al.*^[35] described their initial experience in 16 patients among three sites. One case required conversion to TAMIS due to problems with the glove port. The da Vinci Si platform was utilized. Mean docking and operative duration were 36 (18-75) and 108 (40-180) min, respectively. Patients were positioned prone or left lateral depending on tumor location. Problems included tearing of the glove in four procedures, which required replacement and subsequent completion. There were no cases of peritoneal entry reported, and one patient developed pneumoperitoneum managed conservatively. One patient developed urinary retention requiring catheterization. Median hospital stay was 1.3 days (0-4 days). Positive margins were identified in 2 patients who were found to have more advanced lesions and underwent further resection. No other complications occurred.

Liu *et al.*^[36] described the application of the newest robotic platform, the da Vinci Xi platform (Intuitive Surgical Inc., Sunnyvale, CA), in 34 patients. Lesions were located from 2 to 15 cm from the dentate line and up to 5.5 cm in diameter, average operative time was 100 ± 70 min, and robotic console time was 76 ± 67 min, with a docking time of 25 ± 14 min. Most patients ($n = 32$) were positioned lithotomy versus prone ($n = 2$). There were no intraoperative complications or operative conversions, and the only postoperative complication was a case of *Clostridium difficile* infection in one patient managed medically. Preoperative evaluation consisted of colonoscopy and imaging with use of either endorectal ultrasound or pelvic Magnetic Resonance Imaging (MRI) for local staging. Patients with early-stage rectal neoplasms (uTis or uT1N0M0) and low-risk histology (no lymphovascular invasion) were considered candidates. Patients also included were those with T1 carcinoid tumors, incomplete endoscopically resected rectal polyps, and one case of partial resection for palliative control of bleeding in the setting of metastatic disease^[36]. No patients had received neoadjuvant therapy. The GelPOINT Path port was utilized, and the robotic cart was docked from the side of the patient. A 30° 8-mm robotic camera was placed in the middle trocar and two robotic instruments were used along with an additional assistant trocar. Final pathology yielded 22 (65%) patients with adenoma, 7 (21%) with carcinoma, and 4 (12%) with carcinoid tumors. Three patients were identified as T2 and underwent formal low anterior resection. Notably, severe obesity (BMI > 35) was a predictor of

Table 2. Outcomes of selected cases following robotic TAMIS

Author, Publication	Transanal Port	Patients (n)/ Positioning	Indications (Pathology)	Operative Time (min)/Platform	Tumor Distance from AV (cm)	Tumor Size (cm)	Defect Closure	Margins Positive (n)	Length of Stay (days)	Conversions/ Complications	Recurrence (n)	Follow Up
Hompes et al. ^[35] , <i>Br J Surg</i> 2014	Transanal Glove	16 (15 successful)/prone or left lateral decubitus	6 benign, 4 cancer, 5 scar	median 108 (40-180)/da Vinci Si	median 8 (3-10)	5.3 (0.5-21) cm ²	13 (87%)	2 (13%)	median 1.3 (0-4)	1 conversion to TAMIS; 2 complications (13%)	not recorded	not recorded
Atallah et al. ^[31] , <i>Tech Coloproctal</i> 2015	GelPOINT Path	9/modified dorsal lithotomy	6 benign, 3 malignant	124/da Vinci S or Si	6.6 (3-11)	2.8 (0.9-5.7)	56%	1 (11%)	0.8	1 requiring diagnostic laparoscopy to eval perforation; 2 (22%) complications	0	11.4 months
Liu et al. ^[36] , <i>Surg Endosc</i> 2018	GelPOINT Path	34 (32 lithotomy, 2 prone)	22 benign, 7 malignant, 4 others	100 (±70)/da Vinci Xi	8.6 (±3.6) from dentate line	2.6 (±1.1)	100%	1 (3%)	1.8 (±0.83)	0 conversions; 1 complication	not recorded	188 (±209) days
Tomassi et al. ^[8] , <i>DCR</i> 2019	GelPOINT Path	58 (5 lithotomy, 45 lateral, 8 prone)	18 benign, 28 malignant, 12 others	66.2 (17-180)/da Vinci Si (40) or Xi (18)	8.8 (4-14)	3.3 (1.3-8.2)	100%	3 (5.2%), one fragmented	52 (89.7%), discharged POD 0; 6 (10.3%) discharged POD1	0 conversions; 6 (10.3%) complications	3 (5.5%)	11.5 (0.3-33.3) months
Paull et al. ^[32] , <i>J Robot Surg</i> 2019	SILS and GelPOINT Path	10 da Vinci® Si; 11 Flex® Colorectal Drive/Prone jackknife or high lithotomy	da Vinci: 3 benign, 5 malignant, 1 other Flex: 4 benign, 6 malignant, 1 other	da Vinci Si: 167 (±84.2); Flex Colorectal Drive: 110.1 (±39.9)	da Vinci: 11.1 (±3.8); Flex: 9.58 (±3.6)	not recorded	100% in both	da Vinci: 1 fragmented	not recorded	da Vinci: 4 conversions and 1 complication; Flex: 1 case aborted	da Vinci: 6 months; Flex: not recorded	da Vinci: 6 months; Flex: not recorded
Lee et al. ^[23] , <i>Surg Endosc</i> 2019	GelPOINT Path	19/16 prone, 3 lithotomies	14 benign, 5 malignant	100 (±22)/da Vinci Si or Xi	8.2 (±2.1)	17 (3.2-28.4) cm ²	100%	1 (5.3%)	median 4 (±12) h	0 conversions; 1 complication	not recorded	not recorded
Baker et al. ^[33] , <i>Colorectal Dis</i> 2020	GelPOINT Path	11/all lithotomy	5 benign, 6 malignant	64 (40-100)/da Vinci Xi	7.5 (3-14)	3.6 (2.0-6.0)	6/11 (56%), only full thickness defects	1 (11%)	1 (8 on POD 1, 2 on POD 2, 1 on POD 4)	0 conversions; 1 complication	not recorded	not recorded
Huang et al. ^[37] , <i>Asian J Surg</i> 2020	GelPOINT Path	23/prone	8 benign, 13 malignancy, 2 other	median 107 (15-220)/da Vinci Si (19) or Xi (2)	median 5 (2-8)	median 2.5 (1.1-4.5)	100%	2 (8.7%)	median 3 (1-10)	0 conversions and 0 complications	0	median 9.6 months
Yao et al. ^[34] , <i>Surg Inn</i> 2020	GelPOINT Path	24/lithotomy	3 benign, 15 malignant, 6 others	129.6 (60.0-240.0)/da Vinci Si (7) or Xi (17)	5.9 (3.5-12.0)	median 2.4 (1.0-5.2)	100%	0	4.6 (3-11)	0 conversions and 0 complications	1 (4%)	median 23.6 (4-45) months

Mean unless otherwise stated in column header

significantly longer total operative time, requiring on average twice the operative and robotic console time. Average hospital stay was 1.18 ± 0.83 days, and all patients remained disease-free and alive at follow-up (mean follow-up 188 days), with the exception of the lone patient who underwent palliative resection for bleeding^[36].

Tomassi *et al.*^[8] published their experience with robotic TAMIS in 58 consecutive patients. The first 40 patients were completed with the da Vinci Si platform, and the last 18 with the Xi platform. Patients were most commonly placed in the lateral decubitus hockey stick position ($n = 45$), as opposed to lithotomy ($n = 5$) or prone ($n = 8$), allowing the legs to be moved away from the operative field enabling more range of motion for the robotic arms. While excision was performed as previously described, the proctotomy was closed in a transverse fashion with running 3-0 V-lock Maxon sutures (Medtronic, Minneapolis, MN). Floseal Hemostatic Matrix (Baxter International, Deerfield, IL) was selectively injected below the rectal wall of larger or previously radiated defects. Indications for TAMIS varied widely and included uT1N0 rectal cancer (41.4%), uT2N0 (3.4%), stage III rectal cancer with complete clinical response following neoadjuvant therapy (3.4%), rectal polyps (31%), carcinoid (19%), and GIST (1.7%). Tumor distance from anal verge ranged from 4 to 14 cm and mean operative time on robot was 66 (range 17-180) min. No cases required conversion. Ninety percent of patients were discharged home the same day following surgery, and the remaining patients were discharged on postoperative day 1. Complications included two patients unable to void in recovery and one patient with nausea in a case combined with laparoscopic cholecystectomy. Three patients presented with delayed complications: two patients with lower gastrointestinal bleeding required further endoscopic intervention, and one patient with mucus drainage and tenesmus from suture line dehiscence was treated with antibiotics. Final pathology confirmed preoperative staging in 79.3% of patients, with appropriate oncologic treatment in 88%. Seven patients required further treatment due to upstaging or high-risk features. Fifty-three patients underwent surveillance for a mean follow-up of 11.5 months with 3 local recurrences (5.5%). Overall, 54 (93.1%) have not required radical resection^[8].

HEAD-TO-HEAD COMPARISONS

A single institution head-to-head comparison of conventional and robotic TAMIS was published by Lee *et al.*^[23]. The study was a retrospective analysis of a prospectively collected database of 40 consecutive patients undergoing TAMIS. For conventional resection ($n = 21$), patients were positioned such that the lesion was in the dependent position to allow for laparoscopic suturing. Patients undergoing robotic-assisted resection ($n = 19$) were either in lithotomy or prone depending on tumor location. Platform was selected based on robot availability and surgeon preference. The GelPOINT Path port was utilized for both platforms. Median times for resection were similar between the two platforms, as were for distance of neoplasms from anal verge, R0 resection rate, and indications for resection (with the most common reason being adenoma). Perioperative morbidity was similar as well, with one patient in each group experiencing urinary retention requiring catheterization, and one patient in the conventional group requiring laparoscopic abdominal assistance in repairing a defect with inadvertent peritoneal entry. There were no readmissions or mortalities in either group.

COST

While perioperative and postoperative outcomes appear largely similar, cost appears to consistently favor the use of laparoscopic instruments. The primary cost is the transanal port; the cost of the GelPOINT Path is approximately \$600-800 and the SILS port is \$500^[11,17]. The addition of the robotic platform adds to the cost due to the additional instrumentation.

Hompes *et al.*^[35] identified an additional cost of €837 in comparison to conventional TAMIS. In their head-to-head study, Lee *et al.*^[23] demonstrated an average of \$880 (conventional-\$3563 vs. robotic-\$4440.92). This

was the only difference in outcomes identified between the two procedures. At the Taiwan Medical Center in Taipei, Huang *et al.*^[37] identified an approximate difference of \$2000 in favor of laparoscopy due to their current payment system. It has been proposed that robotic TAMIS may have a supplementary role in more complex rectal lesions in which the gained dexterity of the platform would further support and justify its utility^[41].

FUNCTIONAL OUTCOMES

Overall, TAMIS is very well tolerated^[28,29,45-47]. Studies published thus far have focused only on the conventional platform. Schiphorst *et al.*^[28] examined 37 patients who underwent conventional TAMIS. Patients were placed in lithotomy and the SILS port or the single-site laparoscopic access system (SSL, Ethicon Endo-Surgery, Cincinnati, OH) were utilized for transanal access. Full thickness rectal excisions were performed and defects, when closed, were done so using a V-loc absorbable suture. TAMIS was completed in 36 patients. There were two cases of rectal perforation with peritoneal entry, with one patient converted to laparoscopic anterior resection due to a large rectal defect and pneumoperitoneum. In 7 cases, a hybrid approach with traditional transanal excision was required due to distal lesion location. Three (8%) patients experienced postoperative complications which included hemorrhage ($n = 2$) and abscess ($n = 1$). Long-term morbidity was also experienced in 3 (8%) patients, including local recurrence ($n = 2$) and rectal stricture ($n = 1$). The rectal defect was closed in 27 (73%) patients [Table 2]. Functional outcomes were assessed using the Fecal Incontinence Severity Index (FISI) Score, which takes into account leakage from gas, mucus, liquid and solid stool, and ranges from 0 (total continence) to 61 (complete incontinence). Mean FISI scores before and after surgery decreased from 10 to 5 ($P = 0.01$) at median follow-up of 11 months, consistent with an overall significant improvement in anorectal function following TAMIS. The same cohort was then evaluated again after a median follow-up of 3 years in 44 patients^[45]. Mean preoperative FISI scores were 8.3 (range 0-35) vs. 5.4 (range 0-20) at one-year post-TAMIS ($P = 0.5$). At 3 years, mean FISI score increased to 10.1. This was not statistically significant relative to preoperative FISI. Quality of life was not evaluated in the study.

Sumrien *et al.*^[29] described the Bristol conventional TAMIS series of 28 patients evaluating feasibility and quality of life associated with incontinence. Either the GelPOINT Path or SILS port was used. Full thickness defects were closed. All patients underwent endoscopic evaluation at 3 months along with evaluation of quality of life with the International Consultation on Incontinence Modular Questionnaire (ICIQ). In all, TAMIS was unable to be completed in 3 cases due to extent of tumor. Seventeen cases were performed for benign neoplasia, with R0 resection achieved in 12 (71%). Eleven cases were for malignancy, of which 9 were palliative. In all of these cases, R0 resection was achieved, with one person experiencing recurrence at 11 months. Two patients developed urinary retention and were sent home with a catheter, while 4 patients who developed urinary retention showed resolution prior to discharge. Notably, they modified their practice in favor of a one-time in-out catheterization at the start of the procedure and then noticed a reduction in the incidence of postoperative urinary retention. One patient was readmitted with bleeding at 2 weeks following surgery and managed conservatively. One patient had full thickness perforation amenable to closure by TAMIS. ICIQ was completed in 13 of 26 patients following surgery. Within the questionnaire, the highest score is 60 and a higher score correlates with worsening severity of symptoms. Median score was 15, and 11 of 13 patients scored under 30, while 2 scored higher. They concluded that functional results were consistent with an acceptable quality of life.

Verseveld *et al.*^[46] evaluated quality of life and functional outcomes following TAMIS in 24 patients 6 months following resection. Indications for resection were adenoma ($n = 20$) or low-risk T1 carcinomas ($n = 4$). The SSL port was used for transanal access and patients were in lithotomy. Full thickness excisions were performed and all defects were closed. Mean operative time was 32 (13-94) min and median length of stay was 1 (1-3) day. There was one complication of hemorrhage requiring reoperation. Functional outcomes

were evaluated with the FISIQ questionnaire, and quality of life was evaluated with the EuroQol EQ-5D/EG-VAS and Fecal Incontinence Quality of Life (FIQL) scores. Mean FISIQ did not significantly change pre-resection to six months post-resection. Prior to surgery, 13 patients had abnormal FISIQ scores, while 11 had normal scores. Fifteen patients were continent following surgery, while 5 patients had minor deterioration. These 5 patients also had tumors that were larger and at a shorter distance from the dentate line. FIQL score trended towards improvement following resection and was significantly improved in the area of “coping behavior”. EQ-VAS scores were significantly higher following resection, consistent with an improvement in quality of life, while there was no change in the EQ-5D score, suggesting no change from a social perspective. Overall, the authors concluded that quality of life is generally improved following resection and is equal to the general population at 6 months post-resection.

Karakayali *et al.*^[47] evaluated anorectal function in 10 patients undergoing TAMIS for benign neoplasia or low-risk T1 rectal adenocarcinoma. All procedures were performed in lithotomy, the SILS port was used for transanal access, and all defects were closed. Follow-up consisted of digital rectal examination at 1 week and proctoscopy at 3 weeks following surgery. Anorectal manometry was performed prior to and at 3 weeks following surgery. Mean distance of tumor from anal verge was 5.6 cm (3-10 cm). Mean operative time was 98.8 min. All patients had R0 resections. There were no complications through a mean follow-up period of 27 weeks. Patients were evaluated for function by the Cleveland Clinic Incontinence Score questionnaire. All patients were continent prior to surgery with a score of 0. At 3 weeks postoperative, only one patient complained of incontinence to flatus and fecal urgency for a score of 3. This resolved by 6 weeks following surgery. All 9 other patients had scores of 0. Anorectal manometry prior to surgery was normal for all patients. At postoperative week 3, there were no significant differences seen in mean resting anal pressure, maximum squeeze pressure, or squeeze endurance. However, minimum rectal sensory volume was significantly reduced from 37 ± 8.23 preoperatively to 24 ± 5.15 following surgery ($P = 0.004$). There were no changes in rectoanal inhibitory reflex or sphincter reflex contractions. Thus, the authors concluded that conventional TAMIS is safe without impairment of anorectal function.

LEARNING CURVE

The learning curve for conventional TAMIS appears reasonable and attainable^[27,48,49]. Lee *et al.*^[48] performed at cumulative summation (CUSUM) analysis to determine the number of cases required to reach proficiency. Overall, 254 TAMIS procedures were included with an R1 resection rate of 7%. CUSUM analysis reported that an acceptable R1 rate was achieved between 14 and 24 cases. Clermonts *et al.*^[49] identified a learning curve between 18 to 31 procedures to reach proficiency. They also pointed out that with the establishment of standardized protocols and proctorship a shorter learning curve with fewer cases (6 to 10) may be achieved. Chen *et al.*^[27] reached a similar conclusion, with a minimum of 10 cases required for proficiency. A learning curve has not been established for the robotic platform. In comparison to TEM, our group has evaluated the TEM learning curve, performed by the senior author in 23 patients^[50]. A CUSUM analysis was conducted taking into account the size of lesion and the operating time. The rate of excision was extrapolated. The CUSUM curve stabilized following the four-case mark, after which the rate of excision declined indicating the surmounting of the learning curve.

CONCLUSION

A decade following its introduction, TAMIS appears to be a safe, cost-effective and clinically appropriate approach to the treatment of benign and early malignant (T1) rectal neoplasia with low-risk features. It overcomes several of the limitations of TEM, while matching its efficacy and advantages over resection by traditional TAE. Most importantly, it has an acceptable rate of achieving R0 resection with a low rate of disease recurrence, while maintaining a low rate of morbidity. Oncologic outcomes are not affected should disease recur. The majority of patients are now undergoing TAMIS as an outpatient procedure and many are spared the morbidity associated with TME.

While randomized control trials and head-to-head studies are lacking, the accumulated evidence suggests that the conventional and robotic approaches are similar in their clinical efficacy. However, differences exist and are mostly related to the higher cost of the robotic platform. While proponents of laparoscopy would highlight these cost-related factors, one cannot overlook the improved ergonomics of robotic surgery given the physical constraints of transanal surgery. Also, the gained articulation and dexterity not only allow for easier closure of defects, but may also facilitate the resection of larger lesions in multiple quadrants^[8,36]. Future advancements in robotic technology, particularly with the introduction of single-port robotic systems, will continue to make this platform an attractive alternative in rectal surgery.

It is important to note that in either approach, obesity still remains a factor in contributing to longer operative times^[36,51]. Undoubtedly, transanal surgery will continue to evolve as both conventional and robotic technologies advance and evolve, creating for an everchanging landscape for the colorectal surgeon. Should the clinical efficacy of the two approaches remain similar, the most important factors that remain will then be surgeon preference and comfort level.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Jahansouz C, Arsoniadis EG, Sands DR

Performed data acquisition, as well as provided administrative, technical, and material support: Jahansouz C, Sands DR

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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Large hiatal hernia: minimizing early and long-term complications after minimally invasive repair

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Abstract

Paraesophageal Hernia (PEH) is the protrusion of the stomach and/or other abdominal viscera into the mediastinum due to an enlargement of the diaphragmatic hiatus. The treatment of PEH is challenging: On the one hand, watchful waiting carries the risk of developing acute life-threatening complications requiring an emergency operation. On the other hand, elective repair of PEH has non-negligible morbidity and mortality rates, also due to the characteristics of PEH affected patients, who are generally elder and frail. A review of the literature is presented to highlight strategies that can be adopted to minimize early and long-term complications after PEH surgical repair. The laparoscopic approach has been shown to provide reduced hospital stay, postoperative morbidity and mortality, and overall costs compared to traditional open surgery, and it is currently considered the standard approach both to elective and emergency operations. The evidence suggests that strict adherence to surgical principles, such as hernia sac excision, extended mediastinal dissection of the esophagus, and tension-free crural repair with or without mesh are mandatory to achieve optimal surgical outcomes and reduce PEH recurrence rate. Different shapes, materials, and techniques of prosthetic repair and the use of relaxing incisions have been proposed, but long-term data are lacking, and no conclusions can be drawn regarding the ideal method of crural closure. When a short esophagus is recognized despite extensive mediastinal dissection, esophageal lengthening procedures are indicated. Systematic addition of a fundoplication is strongly encouraged, for either treating gastroesophageal reflux or reducing recurrence rate.

Keywords: Hiatal hernia, paraesophageal hiatal hernia, fundoplication, complications



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INTRODUCTION

Hiatal hernia (HH) is the protrusion of an abdominal organ into the mediastinum through the diaphragmatic hiatus.

There are four main types of HH: Type 1 (“sliding”), the most common, is the herniation of the esophago-gastric junction (EGJ) above the diaphragm, leaving the stomach in the abdomen; Type 2 (“pure paraesophageal”) is the thoracic migration of the gastric fundus while the EGJ remains in the correct position; Type 3 (“mixed”) is a combination of both Type 1 and Type 2 components; and, in Type 4 (“giant”) HH, the herniation involves the entire stomach along with other abdominal viscera, including colon, omentum, small bowel, liver and spleen^[1]. Types 2-4 HH are defined as paraesophageal hernias (PEH) and share the same preoperative work-up and surgical treatment^[2].

Clinical manifestations of PEH include obstructive (dysphagia and postprandial fullness) and compressive (respiratory complications and recurrent pneumonia) symptoms, gastroesophageal reflux (GER) (heartburn and regurgitation), and chronic anemia. PEH can also present acutely with complications: bleeding, acute obstruction, and strangulation resulting in gastric necrosis^[3].

The diagnosis is made with upper endoscopy and barium esophagogram, to assess the morphology of HH. Other examinations, such as computed tomography scan and esophageal manometry, could be helpful in treatment planning, but they are not mandatory^[1,4].

INDICATIONS FOR SURGERY

Elective vs. emergent

In contrast to Type 1 sliding HH, which does not require surgical intervention unless in the presence of severe GER, PEH carries the potential for severe acute complications^[5].

In the past, PEH repair was proposed for all surgically fit patients, regardless of symptoms, due to previous studies demonstrating an unacceptably high mortality rate (ranging 29%-56%), associated with acute presentations^[6,7].

A study from Stylopoulos *et al.*^[8] changed this paradigm. The authors performed a Markov Monte Carlo decision analysis to address the optimal treatment strategy for PEH. The input variables considered, obtained from a systematic review of the literature and data of the 1997 Nationwide Inpatient Sample, were: the estimated mortality rate after elective laparoscopic (1.4%, range 0%-5.2%) and emergency (5.4%) PEH repair, the annual probability of developing symptoms progression (13.8% range 8.1%-21.7%), the annual probability of acute presentation requiring emergency surgery of untreated patients (1.1% range 0.7%-1.9%), and the annual probability of HH recurrence after surgical repair (1.9% range 0.3%-5.4%). With these assumptions, the authors estimated that watchful waiting would be the optimal treatment for 83% of PEH patients, as the risk of developing life-threatening complications is only 1.1% per year.

Since then, other studies have demonstrated lower mortality rates associated with PEH repair, both in the elective and in the emergency setting^[9,10]. Even with these new reports, an updated study using the same statistical methodology achieved the same conclusions in terms of mortality^[11]. However, considering cost-effectiveness, a similar study performed by Morrow *et al.*^[12] concluded that elective repair, although more expensive, guarantees superior quality of life compared to watchful waiting. Current guidelines recommend the elective repair of all symptomatic PEH, while in asymptomatic patients the indications to elective surgery must be balanced with the patient's age and comorbidities^[5].

Open vs. minimally invasive approach

The conventional open approach to PEH repair, through a thoracotomy or a laparotomy, was associated with a high rate of morbidity (5.3%-25%) and mortality (0%-3.7%). The main complications described were pneumonia (2.6%, range 2.1%-8.7%) and wound infections (5.8%, range 0.8%-8.7%)^[13]. Since the introduction of the laparoscopic technique to PEH treatment by Cuschieri^[14] in 1992, the minimally invasive approach has spread rapidly. Several population-based studies demonstrated a significant reduction in hospital stay, intensive care unit stay, postoperative morbidity, mortality, and overall costs of laparoscopic PEH repair compared to the conventional open approach^[15,16]. Therefore, laparoscopy is considered the preferred surgical access for PEH repair, including in the emergency setting^[5,17].

More recently, the robotic platform has been proposed for surgical PEH treatment. The evidence regarding robot-assisted repair of PEH consists of small retrospective series of single institutions in their early experience with this technique, and no long-term follow-up is available. These studies described a postoperative morbidity of 15%-23% and a mortality rate of 0%-2.5%, which are comparable with the outcomes of the laparoscopic series reported in the literature^[18-20].

However, no studies specifically assessing the comparison of robot-assisted and laparoscopic approaches to PEH repair have been conducted, and no clear benefits of the robotic approach have been elucidated yet. Therefore, the role of robotics in the surgical management of PEH remains controversial.

SURGICAL PRINCIPLES

The essential technical steps of the procedure consist of complete reduction of HH, hernia sac excision, extensive mediastinal mobilization of the esophagus, and tension-free crural closure.

The first step of the procedure is the abdominal reduction of HH contents by gentle traction of the hernia sac, proceeding gradually with extensive mediastinal mobilization of the esophagus with blunt dissection in order to obtain at least 2-2.5 cm of intra-abdominal esophageal length [Figure 1A and B]^[21].

During hernia sac dissection, caution must be used to prevent injury to the vagal nerves on the anterior and posterior aspect of the esophagus, to the pleura, and to the adjacent vascular structures [Figure 2]^[22].

After complete reduction, sac excision is imperative [Figure 3]. A tension-free closure of the diaphragmatic crura must be achieved with crural approximation with or without mesh [Figure 4A and B]. Additional technical steps, such as fundoplication, esophageal lengthening, gastropexy, and relaxing incisions, have been investigated to improve the results of PEH repair and are discussed below.

The most common intraoperative complication reported is visceral injury (esophageal and gastric perforations), which is reported in up to 11% of cases, followed by vagal nerve injury and pulmonary complications (pneumonia)^[23].

Sudden increases in intra-abdominal pressure in the immediate postoperative period, due to coughing, belching, vomiting, and lifting weights, have been shown to contribute to PEH recurrence^[24]. Therefore, postoperative nausea and vomiting must be treated aggressively^[5].

Routine early upper gastrointestinal series before starting diet is unhelpful in the absence of suspicious clinical signs, as it has been shown that it would change the clinical management of patients in only 0.8% of cases^[25].

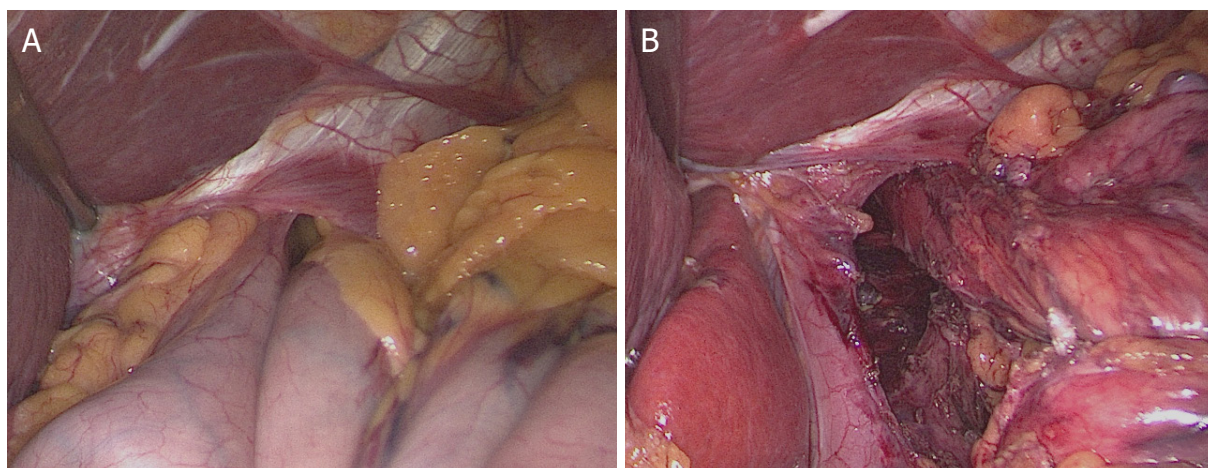


Figure 1. Hernia content reduction: (A) reduction of hiatal hernia contents by gentle traction of the hernia sac; and (B) obtaining at least 2-2.5 cm of intra-abdominal esophageal length

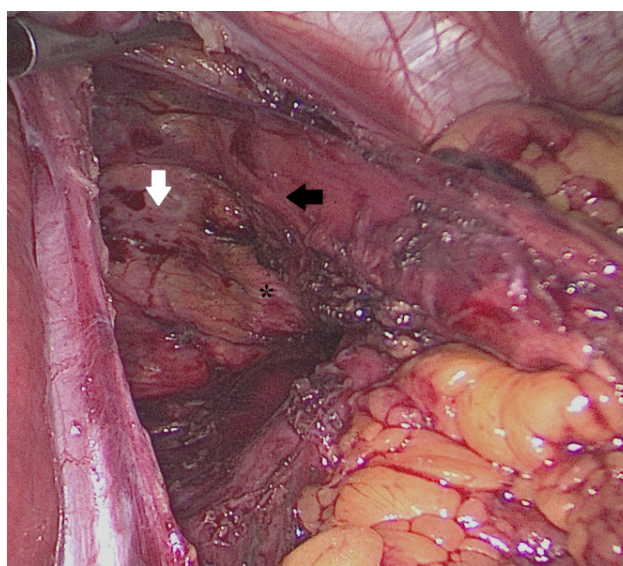


Figure 2. During hernia sac dissection, caution must be used to prevent injury to the vagal nerves on the anterior and posterior aspect of the esophagus, to the pleura, and to the adjacent vascular structures. White arrow, pleura; black arrow, posterior vagus nerve; asterisk, aorta

POSTOPERATIVE COMPLICATIONS

PEH recurrence

A significant rate of recurrences after PEH repair has been reported, although patients are often asymptomatic^[26]. “Radiological” recurrences are described in up to 20%-30% of cases, while only 5% of patients would require surgical revision^[27].

Several technical factors have been investigated in an attempt to reduce the rate of PEH recurrences: PEH sac excision, the method of crural closure, the addition of an esophageal lengthening procedure, and the addition of a gastropexy.

PEH sac excision

To reduce the risk of recurrence, complete excision of the hernia sac should be performed whenever feasible^[28]. This fundamental step of the procedure accomplishes several objectives: first, it represents

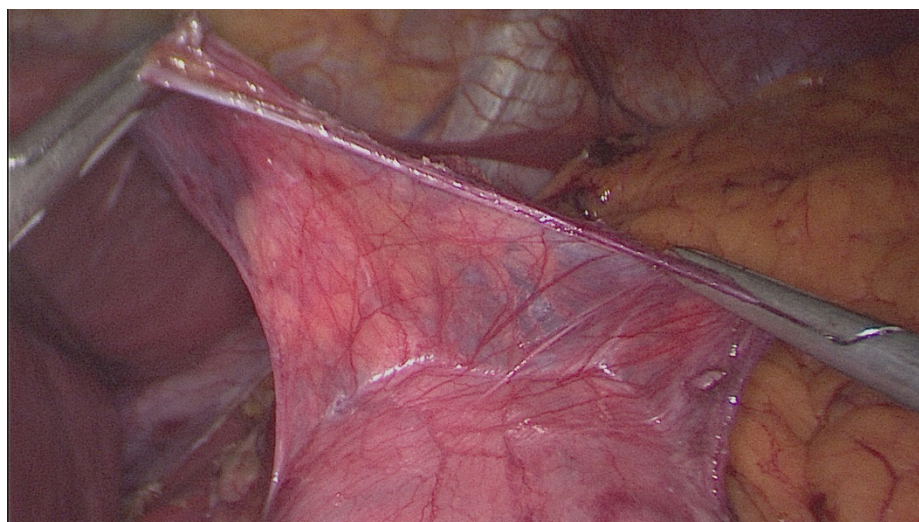


Figure 3. Identification of the hernia sac

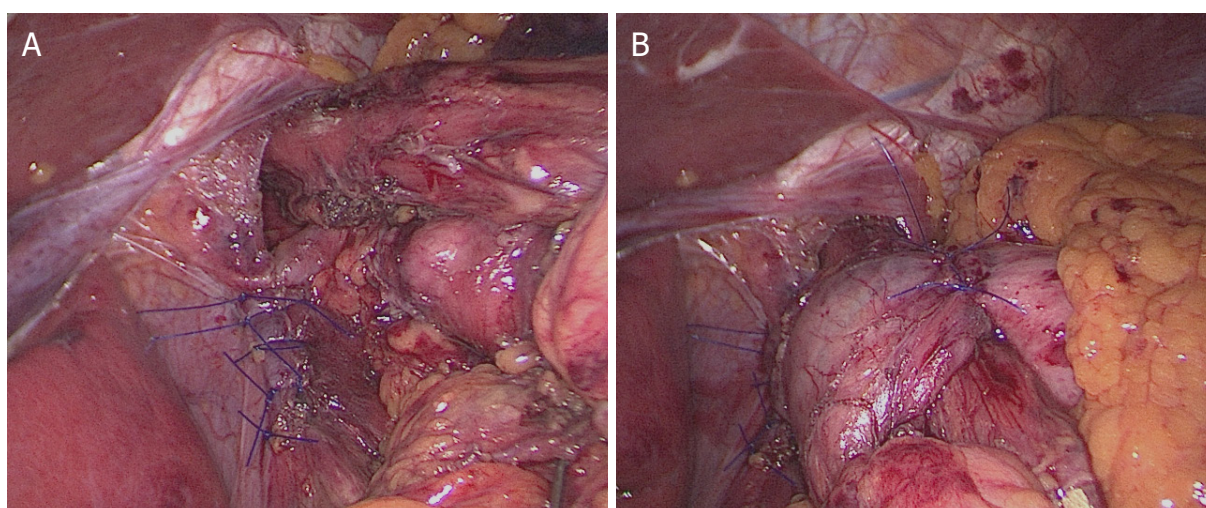


Figure 4. Paraesophageal hernia repair: (A) cruroplasty; and (B) total 360° fundoplication

the correct plane of dissection, avoiding potential injuries to the neural and vascular adjacent structures; second, it reduces the risk of collections in the thoracic cavity; and third, since the hernia sac acts as a lead point that pushes the stomach back in the thoracic cavity, its excision reduces the risk of HH recurrence^[29].

Crural closure: mesh vs. simple cruroplasty

Closure of the diaphragmatic hiatus is mandatory during PEH repair. It can be achieved through several techniques, with primary closure or the use of a mesh. The prosthetic materials can be used as a reinforcement of a primary crural closure or as a “bridge” to close a wide diaphragmatic defect without any attempt to approximate the crural pillars. Moreover, some authors suggest performing crural relaxing incisions to achieve a tension-free crural closure^[30].

In the early laparoscopic series, simple primary cruroplasty was associated with an unacceptably high rate of recurrences at medium follow-up, described in up to 42% of patients^[31].

In light of the good results achieved with the introduction of prosthetic materials in inguinal and ventral repair surgery, the use of meshes has been proposed also in PEH repair. There is a wide array of configurations, materials (including synthetic non-absorbable, absorbable, or biologic matrices), and methods of fixation of the mesh (anterior, posterior, or circumferential, with staples, tacks, sutures, or glue)^[32-36].

Several studies showed a reduced recurrence rate with the use of synthetic meshes. For instance, Frantzides *et al.*^[37] performed in 2002 a randomized controlled trial (RCT) of patients undergoing laparoscopic PEH repair with simple (36 patients) *vs.* reinforced polytetrafluoroethylene (PTFE) cruroplasty (36 patients). The recurrence rate, verified with barium contrast studies, was significantly higher in the simple cruroplasty group compared with the PTFE group (22% *vs.* 0%, $P < 0.006$).

Disadvantages related to the use of synthetic materials include the risk of mesh adhesion, erosion of the esophageal wall, and extensive fibrosis resulting in the onset of troublesome dysphagia^[38].

Biological and absorbable meshes have been proposed to overcome the downsides of synthetic meshes. Oelschlager *et al.*^[39] performed a multicenter RCT to test the efficacy of crural reinforcement with a biological mesh derived from porcine small intestinal submucosa (51 patients) compared to primary crural closure (57 patients). The authors published in 2006 the phase 1 results of the trial, showing a significant reduction in radiological PEH recurrences compared to primary repair (9% *vs.* 24%) at six-month follow-up. However, a longer follow-up of the same study showed a high rate of recurrences, with no significant differences between the two groups (59% in the mesh group *vs.* 54% in the primary repair group)^[40].

The short-term results of biological meshes were also confirmed in a systematic review and meta-analysis performed by Antoniou *et al.*^[41] including five studies comparing simple suture *vs.* biologic mesh cruroplasty. However, no long-term data were available for analysis.

Watson *et al.*^[42] performed a multicenter RCT in 2015 with the aim of comparing three methods of PEH repair: primary suture (43 patients), absorbable mesh (41 patients), and non-absorbable mesh (42 patients) cruroplasty. A combined radiological and endoscopic assessment of recurrences was performed at 12-month follow-up, and no significant difference was found among the three groups. These results were also confirmed at five-year follow-up^[43].

Several meta-analyses described a significant reduction in the recurrence rate at medium-term follow-up, including a lower risk of surgical revision, with the use of prosthetic materials, but the quality of analyzed data was poor and therefore the results are of limited level of evidence^[44,45]. For instance, Tam *et al.*^[46] performed in 2016 a systematic review and meta-analysis of studies assessing the comparison between primary repair and the use of synthetic mesh. They reviewed 13 publications including RCTs and observational studies. The overall recurrence rate was found to be 24% (91/382) for the suture group compared to 13% (46/354) for the mesh group. However, follow-up was significantly shorter, with only half of the patients available for follow-up in the mesh group, therefore recurrences could be underestimated. The authors concluded that the available evidence is of low quality and high risk of bias and does not allow drawing definitive conclusions.

Furthermore, more recent series comparing primary *vs.* mesh reinforced cruroplasty have shown similar outcomes in terms of recurrences at long-term follow-up^[47,48]. For instance, Koetje *et al.*^[49] reported the comparison between primary repair (127 patients) and mesh reinforced (62 patients) cruroplasty with a follow-up of 40 months. The overall rate of radiological recurrence was similar between the two groups (25.8% mesh *vs.* 23.6% no mesh), with similar reoperation and symptomatic recurrence rates.

To date, there is no high-level objective evidence recommending the use of meshes in PEH surgical treatment, nor demonstrating the superiority of a specific technique over another. The ideal mesh does not exist, and the choice of the technique largely depends on the surgeon's preferences^[50,51]. Current guidelines admit that no recommendations can be made regarding the use of mesh in PEH repair^[5].

"Short esophagus" and esophageal lengthening

The entity of the "short esophagus" (SE) is debated. SE is defined as less than 2-2.5 cm of intra-abdominal esophageal length after extensive mediastinal dissection^[52]. The estimated incidence of the SE is reported to be 1.9%-20% and is thought to be caused by fibrosis and scarring of chronic severe GER insult^[4]. Some authors question the real existence of SE, claiming the presence of "apparent" SE: a normal-length esophagus that is folded into the chest and appears to be short before extensive mediastinal mobilization^[53]. The use of routine intraoperative endoscopy during PEH repair is suggested to detect SE^[54].

When a "real" SE is recognized intraoperatively, esophageal lengthening procedures, such as Collis-Nissen fundoplication, are indicated^[55]. The current technique consists of a totally laparoscopic gastropasty, performed with a circular stapler, to create a trans-gastric window, through which a linear stapler is introduced to create the "neo-esophagus"^[56]. The results of this procedure, performed with the laparoscopic approach, are similar to those reported with the open technique, with a recurrence rate of 25-13%^[4].

However, Collis-Nissen fundoplication is a challenging procedure, with a reported morbidity rate of 19%-36%, including atelectasis, pneumonia, pneumothorax, and pleural effusion^[57]. Moreover, it carries a higher risk of leak compared to fundoplication alone (2.7% vs. 0.6%)^[58].

Anterior gastropexy

Anterior gastropexy was first described by Boerema in 1969, but it was abandoned due to a reported excessively high risk of recurrence, which occurred in 60% of patients^[59,60]. With the recognition of the importance of the fundamental technical steps of the procedure, such as sac dissection and excision, that were not performed at the time of the original Boerema procedure, this technique has been modified and proposed again. To date, there are limited data regarding the role of anterior gastropexy, in particular without associated procedures such as mesh cruroplasty or fundoplication, in PEH surgical treatment [Table 1]. Only Daigle *et al.*^[68] performed a multicenter study of 101 PEH repair with anterior gastropexy without fundoplication, showing an acceptable recurrence rate of 16.8% at 12-month follow-up and avoiding complications of mesh positioning and anti-reflux procedures. However, 29.7% of patients experienced some degree of postoperative GER.

More recently, several authors have described the use of this procedure in the acute setting or in high-risk patients^[68,70]. In these situations, the procedure was considered attractive because it does not require long operative times or advanced technical skills even with the minimally invasive approach, and does not affect the possibility to perform subsequent elective PEH repair.

For instance, Yates *et al.*^[69] reported the results of 11 high operative risk patients presented with acute gastric volvulus and treated with laparoscopic anterior gastropexy. There were no intraoperative complications, but two patients required reintervention. The authors concluded that laparoscopic anterior gastropexy could be considered a valid surgical alternative for frail patients.

Gastroesophageal reflux

The systematic or tailored addition of a fundoplication during PEH repair is a matter of debate.

Table 1. Outcomes of laparoscopic gastropexy in paraesophageal hernia treatment

Authors	Year	n	GP (n)	Associated procedures (n)	Recurrences (%)	Mortality (%)	Follow-up (months)	Notes
Agwunobi <i>et al.</i> ^[61]	1998	13 HR	13		14.4% symptomatic	7.7	10	15.4% conversions
Hawasli <i>et al.</i> ^[62]	1998	27	25	MC = 25	0%	0	1-56	22.2% reflux
Van der Peet <i>et al.</i> ^[63]	2000	19	19	SC = 17 MC = 2 FP = 15	15.8% radiological	0	24	15.8% conversions 75% reflux esophagitis without FP
Ponsky <i>et al.</i> ^[64]	2003	28	28	FP = 28	0% radiological	0	12	
Diaz <i>et al.</i> ^[65]	2003	116	48	SC = 110 MC = 6 FP = 114 EL = 6	32% radiological	1.7	30	4.3% major complications
Horstmann <i>et al.</i> ^[66]	2004	16	16	MC = 16 FP = 16	0% radiological	0	14	6.25% conversions 31% pleural injury
Poncet <i>et al.</i> ^[67]	2010	89	77	MC = 89 FP = 89	15.7% radiological	0	57.5	4.4% conversions 7.8% morbidity
Daigle <i>et al.</i> ^[68]	2015	101	101	SC = 94	16.8% endoscopic/ radiological	0	10.9	22% morbidity 29.7% reflux
Yates <i>et al.</i> ^[69]	2015	11 HR	10	TG = 11	0% symptomatic	N/A	3	2 readmissions 2 TG dislocations
Higashi <i>et al.</i> ^[70]	2017	8 HR	100		0% symptomatic	0%	48	

HR: high risk patients; GP: gastropexy; MC: mesh cruroplasty; SC: simple cruroplasty; FP: fundoplication; EL: esophageal lengthening; TG: tube gastrostomy

The rationale for adding a fundoplication is twofold: treating preoperative GER symptoms and preventing the postoperative onset of GER. GER is a frequent clinical manifestation of PEH because the herniation through the diaphragmatic hiatus determines a functional incompetence of the lower esophageal sphincter (LES), favoring the reflux of the gastric contents. GER can also occur “*de novo*” postoperatively due to altered functional anatomy of the GEJ caused by extensive mediastinal dissection. Furthermore, fundoplication is thought to anchor the cardia below the diaphragm, contributing to the reduction in the rate of recurrences^[50]. For these reasons, some authors advocate the routine addition of a fundoplication to restore the functional competence of the LES^[71].

Other authors sustain the selective addition of fundoplication during PEH repair depending on the presence of preoperative GER or altered esophageal motility at esophageal manometry. They believe that the intra-abdominal reduction of PEH restores the normal anatomy of the EGJ, therefore no other anti-reflux operations, with the consequent risk of dysphagia, are needed^[72].

However, the LES competence can be difficult to assess preoperatively, because esophageal manometry can be unreliable in the presence of PEH^[73]. Furthermore, the incidence of dysphagia following fundoplication is minimal in experienced hands^[74].

Müller-Stich *et al.*^[75] performed a RCT comparing mesh-augmented hiatoplasty with or without the addition of a fundoplication. At 12-month follow-up, the fundoplication group had a significantly lower incidence of GER symptoms than hiatoplasty alone, and the subjective results were confirmed by objective upper endoscopy findings. Interestingly, the incidence of gas bloat and dysphagia did not differ between the two groups, leading the authors to favor the systematic addition of an anti-reflux procedure.

In addition, Furnée *et al.*^[76] performed a comparative study of patients who underwent PEH repair with or without fundoplication. Of the 20 patients who did not receive fundoplication, new onset of esophagitis occurred in 28%, and pathological acid exposure was demonstrated in 39%. In the fundoplication group, 8.7% of patients experienced dysphagia. The authors concluded that, since the rate of postoperative side effects of fundoplication is low, while objective evidence of postoperatively *de novo* onset of GER occurred frequently, the addition of a fundoplication should be recommended during PEH repair.

To date, there is no consensus on the type of wrap and on the fixation of the fundoplication to the esophagus or the diaphragmatic pillars^[28]. In a systematic review of the literature, including 24 studies, Andolfi *et al.*^[77] concluded that the preferred approach should be a total fundoplication when the esophageal motility is normal.

CONCLUSION

The current review of the literature shows that the controversies regarding the optimal repair of paraesophageal hernia, including the best technique for crural closure, the addition of a fundoplication, and of esophageal lengthening procedures, remain unresolved. The wide heterogeneity of techniques and materials, together with the low incidence of PEH, makes it difficult to investigate the specific role of the single technical factors concurring in PEH repair.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Uglicione E, Rebecchi F

Performed data acquisition, as well as provided administrative, technical, and material support: Seno E, Morino M

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All authors declared that there are no conflicts of interest.

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Review

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Sublobar resection in high-risk patients for lobectomy: current and future strategy

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Abstract

Surgical resection by lobectomy is the gold standard of therapy for early stage non-small cell lung cancer. However, not all patients are medically fit to undergo surgery. In patients considered high-risk for lobectomy, alternative strategies have been developed including radiofrequency ablation, cryoablation, microwave ablation, stereotactic radiation therapy, wedge resection, and segmentectomy. This work reviews the definition of high-risk, and the outcomes that have been associated with each treatment technique. Some technical points regarding wedge resection versus segmentectomy are noted. Future directions are discussed in the context of treatment for patients considered at high-risk for lobectomy.

Keywords: Non-small cell lung cancer, sublobar resection, surgical technique, high-risk patients

INTRODUCTION

This work is intended to review the current literature surrounding the definition of a patient with lung-cancer who is considered high-risk for lobectomy, discuss different treatment modalities and their outcomes for these patients, and note some potential future directions and their benefits to high-risk patients. PubMed and EMBASE were reviewed and works were included based on relevance. Previous work in this field has involved clinical trials to determine patients who are considered high-risk, their results with sublobar resection, radiofrequency ablation (RFA), cryoablation, microwave ablation (MWA), stereotactic body radiation therapy (SBRT), and comparisons of these alternative techniques against sublobar resection.



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Technical aspects of wedge resection and segmentectomy are discussed for high-risk patients, and future directions of lung cancer treatment that could specifically benefit high-risk patients are noted.

DEFINITION OF HIGH-RISK

One of the most used definitions for high-risk patients come from the American College of Surgeons Oncology Group (ACOSOG) Z4032 trial of stage I non-small cell lung cancer (NSCLC), with tumors ≤ 3 cm, that focused on clinical details to define high risk^[1]. Patients were considered high-risk for sublobar resection, or sublobar resection with brachytherapy, if their pulmonary function tests (PFTs) showed a Forced Expiratory Volume in 1 second (FEV1) $\leq 50\%$ of predicted, or if their Diffusing Capacity for Carbon Monoxide (DLCO) was $\leq 50\%$ of predicted, or if they met two of the following criteria: age ≥ 75 years, FEV1 51%-60% predicted, DLCO 51%-60%, diagnosed with pulmonary hypertension (pulmonary artery systolic greater > 40 mmHg) as estimated by echocardiography or right heart catheterization, left ventricular ejection fraction $\leq 40\%$, resting or exercise arterial $pO_2 \leq 55$ mmHg or $SpO_2 \leq 88\%$, $pCO_2 > 45$ mmHg, or Modified Medical Research Council Dyspnea Scale score ≥ 3 .

However, while ACOSOG Z4032 provides a precise definition, controversy still exists. Puri *et al.*^[2] reported the non-propensity score matched findings of their review of 1066 patients from the Washington University School of Medicine. They found that perioperative outcomes for the high-risk group by ACOSOG Z4032 were not different from normal-risk patients - respiratory failure, 4% (7/194) in high risk *vs.* 5% (41/872) in normal risk ($P = 0.70$); prolonged air leak of > 5 days, 8% (16/194) in high risk *vs.* 6% (54/872) in normal risk ($P = 0.36$); and 30 day/hospital mortality 1% (2/194) in high risk *vs.* 2% (14/872) in normal risk ($P = 0.75$). The most recent National Comprehensive Cancer Network NSCLC guidelines focus on a definition of high-risk that is aimed at risk of recurrence and leaves the definition of 'operative' high-risk unresolved^[3].

PERI-OPERATIVE OUTCOMES OF HIGH-RISK PATIENTS UNDERGOING SUBLOBAR

RESECTION

Fernando *et al.*^[4] reported perioperative outcomes for their high-risk patients in 2011. Three deaths (1.4%, 3/222), one in the sublobar resection group and two in the sublobar resection with brachytherapy group, occurred within 30 days. Three more deaths occurred by 90 days (2.7% 6/222), and four of the deaths within 90 days were attributed to the surgery performed. Kent *et al.*^[5] provided a further operative and pathologic analysis of this patient group in 2013. When segmentectomy ($n = 57$ patients) was compared to wedge resection ($n = 153$ patients), they found that segmentectomies had better margin size than wedge resections, median 1.5 cm (range 0.1-6.5 cm) *vs.* 0.8 cm (0-3.6 cm), $P = 0.0001$; greater number of lymph node stations sampled, median 3 (0-6) *vs.* 1 (0-6), $P < 0.0001$; and greater number of lymph nodes removed, median 4 (0-20) *vs.* 1 (0-23), $P < 0.0001$.

Sancheti *et al.*^[6] reported on their institution's experience with 'high-risk' patients defined by ACOSOG Z4032. The study focused on Stage I NSCLC and, in their sub-analysis of patients who underwent sublobar resection, reported shorter operative time in the high-risk group *vs.* standard risk group, median 89.0 min (range 64.0-110.0) *vs.* 112.5 min (74.0-145.5), $P = 0.04$; but longer length of stay, median 4 days (3-7) in the high risk group *vs.* median 3 days (2-5) in the standard risk group, $P = 0.003$. They found no statistical difference in total patient numbers with major morbidity, 12.3% (7/57) high risk group *vs.* 6.7% (4/40) standard risk group, $P = 0.39$; but, noted more patients with minor morbidity in the high-risk group, 43.9% (25/57) *vs.* 20% (12/60) in the standard risk group, $P = 0.02$. The 3-year survival from sublobar resection was worse for high risk patients than standard risk patients, 57% *vs.* 71%, but not statistically significant, $P = 0.15$.

Lastly, Puri *et al.*'s^[2] sub-analysis of their high-risk patients who underwent sublobar resection found no differences in perioperative outcomes between high-risk patients ($n = 72$) and normal-risk patients ($n = 112$). Atrial fibrillation was slightly more common in the high-risk group than normal-risk, 11% (8/72) vs. 6% (7/112), $P = 0.28$, but this was potentially due to low event rates in both groups. They did not report the sublobar resection group survival Kaplan-Meier curves, but noted on logistic regression analysis that ACOSOG Z4032 high-risk status was not associated with the risk of perioperative complications (data not provided in their manuscript)^[1,2].

THERAPEUTIC CHOICE FOR OPTIMAL LONG-TERM OUTCOMES OF HIGH-RISK PATIENTS

Since Ginsberg *et al.*'s^[7] 1995 report on the Lung Cancer Study Group's randomized control trial of lobectomy vs. limited resection for T1 NSCLC, lobectomy has remained the gold standard for resection of early stage lung cancer. However, the current NCCN guidelines state that anatomic pulmonary resection is the preferred method for the majority of patients with NSCLC^[3,7]. The NCCN guidelines further elaborate on sublobar resection as being appropriate in the setting of "poor pulmonary reserve or other major comorbidity that contraindicates lobectomy", while noting that SBRT is recommended for medically inoperable patients or patients who refuse surgery^[3]. As there is no clear definition for "high-risk" patients, the choice of therapy for high-risk patients remains the purview of the clinicians treating the patient. Ablation techniques, SBRT, and lobectomy continue to be options for high-risk patients, in addition to sublobar resection.

Multiple ablation techniques have been reported for lung cancer including RFA, microwave ablation, and cryoablation^[8-10]. In 2005, Fernando *et al.*^[8] reported RFA as an alternative for patients with peripheral lung cancer who are not surgical candidates. In their initial 18 patient series with 21 total tumors, they treated patients of all stages with a median tumor size of 1.8 cm (range 1.2-4.5 cm). In this broad patient set, they noted a mean progression-free survival of 16.8 months. In 2007, Simon *et al.*^[11] published their 153 patient series from 1998-2005 that reviewed the outcomes of patients treated with RFA who were refused surgery or were not deemed suitable as surgical candidates. The 5-year survival rate for stage I NSCLC was 27%, with local progression-free rate for tumors ≤ 3 cm equal to 47%, and for > 3 cm equal to 25%. A recent review of the National Cancer Database compared SBRT to RFA for stage I NSCLC (4,454 SBRT vs. 335 RFA patients)^[12]. RFA patients were noted to have more comorbidities than SBRT patients. They performed a propensity score matching and found no difference in the overall survival rate (OS) at 1-, 3-, and 5- years (31.9% SBRT vs. 27.1% RFA, $P = 0.835$).

MWA is another thermal ablation technique that uses high temperature to destroy tumors^[9]. Zhong *et al.*^[9] reported on 113 patients who underwent microwave ablation; 35 patients had early stage disease and 78 patients had late stage lung cancer. 10.6% (12/133) of all patients had a pneumothorax after the procedure, but no intraoperative or perioperative deaths were observed. At 3 years, they reported that the survival of the early stage group was 84.7%, in comparison to 71.7% in the advanced stage group, $P = 0.576$. Zhao *et al.*^[13] reported a longer-term follow-up (out to 5 years) of 34 early stage patients (T1a-T3N0M0). Pneumothorax was noted in 24 cases (59%) with 6 cases requiring chest tube insertion (15%). Their 5-year overall survival rate was 46.7%. Yuan *et al.*^[14] performed a meta-analysis of 53 studies to compare outcomes of RFA with MWA for primary lung cancer and pulmonary metastases. They found a pooled pneumothorax rate of 34.3% (95%CI: 25.9%-43.1%) in the RFA group vs. 33.9% (95%CI: 23.8%-44.8%) in the MWA group, $P = 0.957$. Severe pneumothorax that required intervention occurred in 12.3% of patients (95%CI: 6.8%-19.1%) in the RFA group and in 11.0% of patients (95%CI: 4.5%-19.7%) in the MWA group, $P = 0.797$. Based on the 8 studies for RFA and 6 studies for MWA, they found comparable median OS for the 2 groups, RFA 28.4 months (95%CI: 20.9-35.8) vs. MWA 24.4 months (95%CI: 16.9-31.8).

Cryoablation is the other common ablative technique and works by creating a freezing zone that first freezes the extracellular fluid and then the intracellular fluid, causing cellular and tissue destruction during multiple cycles with temperature ranges typically in the -20°C to -40°C range^[15,16]. For Stage I NSCLC, Yamauchi *et al.*^[17] reported a 3-year overall survival of 88% and a disease-free 3-year survival of 67%, while Moore *et al.*^[18] reported a 5-year overall survival of $67.8\% \pm 15.3$, cancer-specific survival of $56.6\% \pm 16.5$, and 5-year progression-free survival rate of $87.9\% \pm 9$. Yamauchi reported pneumothorax in 28% cases (7/25) vs. Moore's report of 51.0% (24/45); and each reported 1 case requiring chest tube insertion. Zemlyak *et al.*^[19] performed a small retrospective, non-propensity matched comparison between sublobar resection ($n = 25$), radiofrequency ablation ($n = 12$) and percutaneous cryoablation ($n = 27$) and found that the 3-year overall survival was 87.1%, 87.5%, and 77%, respectively, $P > 0.05$. Additionally, the 3-year cancer-specific and cancer-free survival for sublobar resection, radiofrequency ablation, and percutaneous cryoablation groups was 90.6% and 60.8%, 87.5% and 50%, and 90.2% and 45.6%, respectively with $P > 0.05$ for intergroup comparisons of 3-year cancer specific survival and 3-year cancer free survival. They noted that the lack of significance was likely due to a small sample size.

The American Society of Radiation Oncology defines SBRT as ablation radiation doses in 1-5 fractions with high conformal techniques^[20]. They note in these consensus guidelines that stage I NSCLC patients with “high operative risk” should be offered SBRT as an alternative to sublobar resection, but the longer-term outcomes over 3 years are not well-established. Some of the longest survival data for SBRT comes from a follow-up of the North Central Cancer Trials Group N0927 randomized phase II study, comparing 34 Gy vs. 48 Gy SBRT for medically inoperable stage I peripheral NSCLC^[21-22]. They found that the 5-year overall survival in the 34 Gy and 48 Gy groups were 29.6% (95%CI: 16.2%-44.4%) and 41.1% (95%CI: 26.6%-55.1%) respectively. Progression-free survival at 5 years was 19.1% (95%CI: 8.5%-33.0%) and 33.3% (95%CI: 20.2%-47.0%) for the 34 Gy and 48 Gy groups respectively. A recent systematic review and pooled analysis compared RFA to SBRT, and found that SBRT has better 5 year local tumor control rate, 42% (95%CI: 30%-54%) RFA vs. 86% (95%CI: 85%-88%) SBRT $P < 0.001$; but similar OS, 32% (95%CI: 22%-43%) for RFA vs. 40% (95%CI: 36%-45%) for SBRT $P = 0.41$ ^[23]. In 2019, Ager *et al.*^[24] reviewed the National Cancer Database and compared 14,651 SBRT patients to 1141 patients who underwent some form of percutaneous local tumor ablation therapy (LTA). After propensity score matching, their Cox modeling found a hazard ratio of 0.83, 95%CI: 0.73-0.94, $P = 0.002$, showing improved survival for SBRT patients. Adjusted rates of OS at 5 years were 31.0% and 26.2% for SBRT and LTA, respectively. Chi *et al.*^[25] also reviewed the National Cancer Database and compared SBRT to multiple different forms of surgery for early stage lung cancer. They found that the 5-year overall survival for the resection groups ranged from 48.1% (wedge resection) to 64.6% (lobectomy), compared to 30.4% in the SBRT cohort, $P < 0.01$ for each resection type vs. SBRT. Their Cox model hazard ratios for wedge resection, segmentectomy, and lobectomy compared to SBRT demonstrated improved overall survival with surgery with values from 0.55 (wedge resection) to 0.40 (lobectomy), each P value < 0.01 .

In terms of surgical treatment, Jensik *et al.*^[26] were the first to propose segmentectomy as an appropriate alternative to lobectomy for small-sized lung cancers. Since then, the debate has continued with findings for and against this in randomized trials, large database studies, and meta-analysis reviews, with lobectomy continuing as the standard of care with allowances for sublobar resection of high-risk cases^[3,7,27,28]. Relatively few studies have focused on direct comparisons of surgical options in high-risk patients. Ijsseldijk *et al.*^[28] recently published a comprehensive systematic review and meta-analysis of 100 studies comparing SBRT, sublobar resection, and lobectomy. In this work, they found that lobar resection had a 5-year OS of 74% [0.69, 0.78], sublobar resection had a 70% OS [0.64, 0.77], and SBRT had a 46% OS [0.35, 0.57], with both surgical survivals statistically better compared to SBRT, both $P < 0.01$. Disease-free survival at 5 years in patients who had lobar resection was 76% [0.71, 0.82], sublobar resection was 71% [0.67, 0.76], and SBRT was 46% [0.35, 0.57], with both surgical survivals statistically better compared to SBRT, $P < 0.01$. However,

this work was not specified to include only high-risk patients. Hou *et al.*^[29] performed a specified meta-analysis directly comparing segmentectomy to sublobar resection for high-risk patients in 9 studies. They noted heterogeneous definitions for what qualified as high-risk, but most studies had followed Fernando *et al.*'s^[1] criteria from their 2011 work mentioned earlier in this review. For OS, Hou *et al.*^[29] included 7 studies, and on meta-analysis found that the hazard ratio for segmentectomy compared to wedge resection for stage I NSCLC was 0.80 in favor of improved OS with segmentectomy compared to wedge resection [95%CI: 0.68-0.93; $P = 0.004$]. On subgroup analysis, there was comparable OS for stage I tumors ≤ 2 cm; however, the hazard ratio favored improved OS with segmentectomy compared to wedge resection, 0.39 [95%CI: 0.15-1.02; $P = 0.06$]^[29]. Cancer-specific survival also favored segmentectomy over wedge resection, hazard ratio 0.42 [95%CI: 0.20-0.88; $P = 0.02$]. They were unable to fully assess disease-free survival as only 3 studies reported data that was usable for comparison.

Unfortunately, even with all this data, the best option for high-risk patients who can undergo limited resection, but not full lobectomy, remains unclear. Three randomized control trials are ongoing comparing lobectomy to sublobar resection for early stage NSCLC, ≤ 2 cm with No lymph node status^[30-32]. All three studies have reported their peri-operative safety results and found no substantial differences. Suzuki *et al.*^[30] noted a higher airleak rate in their 552 segmentectomy patients compared to their 554 lobectomy patients, 6.5% *vs.* 3.8%, $P = 0.04$. However, Altorki *et al.*'s^[31] report did not note an increased airleak in their sublobar resection group, 340 patients total, compared to their 357 lobectomy patients. This was despite including wedge resections and segmentectomies in their sublobar resection group; 201 wedge resection patients and 139 lobectomy patients^[31]. Stamatis *et al.*^[32] noted equal rates of prolonged air leak in their 53 segmentectomy patients compared to their 54 lobectomy patients. Until the long-term outcomes of these randomized control trials are evaluated, the choice of therapy should be determined by a multidisciplinary team. Surgical resection, when feasible and preferably segmentectomy, remains the recommended treatment if lobectomy is not possible^[3].

SUBLOBAR RESECTION TECHNICAL POINTS: WEDGE RESECTION VS SEGMENTECTOMY

Patient selection remains of paramount importance for surgical procedure choice. Wedge resection and segmentectomy are most appropriate for smaller, peripherally located lesions away from the hilum of the lung. Segmentectomy should be favored when possible given its respect for anatomic planes, but comes with a caveat. The target lesion must lie within the boundaries of one segment or group of segments. One of the authors has written extensively regarding this process and reported that patients with lesions under 2 cm that are resected with segmentectomy have no difference in outcomes compared to the patients treated with lobectomy^[33-35]. Segmentectomies are more technically challenging as the surgeon must create a fissure between segments and then dissect out and ligate the segmental vessels and bronchus. Wedge resection is performed without respect to anatomic planes or specific vessels, but can be useful when the target lesion is very small (1 cm or less), subpleural, or crosses segmental borders. Care should be taken to ensure that the margins from the edge of the tumor to the final staple line are appropriately wide to minimize recurrence and that adequate lymph nodes are removed to ensure accurate staging^[36-38].

FUTURE DIRECTIONS

Radiomics is a rapidly growing field in which radiographic images are used to determine features such as lesion shape, volume, texture, attenuation, and other factors that are not readily apparent or are too difficult for an individual radiologist to assess visually or qualitatively^[39]. Radiomics is being studied to predict histologic subtypes, specific mutations, and benefit of adjuvant chemotherapy after resection^[40-42]. Radiomics has already been used to predict OS in NSCLC; specifically, the recurrence of NSCLC after SBRT^[43-45]. Radiomics may even be able to predict survival based on resection type and offer high-risk patients more tailored care.

Another advancement lies in improved lesion targeting for NSCLC that is not located at the outermost periphery. Image-guided video-assisted thoracoscopic surgery (iVATS) is an emerging technology that is being developed to allow localization of non-palpable lesions^[44]. Early reports indicate excellent rates of localization using modifications of previously developed techniques with wires, microcoils, and indocyanine green with near-infrared imaging^[46-48]. These lesions are then removed with sublobar resections. Of note, the use of this technology requires a hybrid operating room equipped with a CT scanner, which is not available at all facilities. By being able to remove deeper lesions while still performing wedge resection or segmentectomy, iVATS offers high-risk patients another surgical option for lesions that previously may have required lobectomy.

CONCLUSION

In summary, high-risk patients remain a poorly defined group, with patients typically defined as those with some degree of poor pulmonary function and often other significant functional or medical limitations. In these patients, surgical resection is the gold standard relative to SBRT and ablative techniques. Segmentectomy should be performed rather than wedge resection when feasible, and when lobectomy is not an option. Future developments in radiomics and iVATS technique may help further refine the optimal treatment approaches for high-risk patients.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, performed data analysis and interpretation, data acquisition, as well as provided administrative, technical and material support: Dolan D, Swanson S

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Dr. Swanson reports receipt of honoraria from Covidien and Ethicon for speaking and consulting services.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Editorial

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Metabolic and bariatric surgery

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Obesity is a disease causing multiple comorbid health conditions such as type 2 diabetes, hypertension, obstructive sleep apnea, back pain, and cancers. Weight loss improves overall health and quality of life. When diets, exercise, and behavioral changes are not enough, weight loss operations can help patients lose 100 pounds or more, reverse associated health problems, and increase longevity.

In the past year, COVID-19 has affected over 1.6 million people worldwide, with over 300,000 deaths in the United States alone. During this time, we have learned a lot about inflammation and response to COVID-19. We have known that obesity creates a chronic inflammatory state and that it contributes to many other diseases such as diabetes. However, during the COVID-19 pandemic, we have witnessed that patients who are overweight and with weight-related illness are at higher risk of death after exposure to the coronavirus. With a vaccine released this week, we are all hopeful for immunity. We are also more mindful than before about the effects of obesity on health and wellbeing.

The *Mini-invasive Surgery* Journal sought to have a Special Issue for “Metabolic and Bariatric Surgery.” This is a bold initiative with so many other outlets to publish manuscripts on the topic. When the Journal asked me to co-edit the volume, I was intrigued. We recruited authors from around the world to share their observations, science, and reviews of the literature. I am very grateful to those authors who managed to contribute despite the pandemic considering the added demands on providers.

In this volume, Dr. Rami Lutfi^[1] summarized the current status of metabolic surgery. He emphasized that bariatric operations are treating diabetes. He reviewed the STAMPEDE trial, 2nd Diabetes Surgery Summit, and guidelines from the American Diabetes Association. He also reviewed the choice of different operations.



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For lower weights, endoscopic therapy is evolving. Mlabasati *et al.*^[2] at BIDMC shared lessons learned setting up an Endoscopic Bariatric multidisciplinary program to provide intragastric balloon and endoplication for obesity. Dr. Aurora Pryor^[3] reviewed the endoscopic approaches to treating complications of bariatric surgery. She noted a 4%-10% complication rate in the first month after bariatric surgery. She went on to describe endoscopic treatments for complications of bleeding, strictures, ulcer, reflux, and weight regain. With endoscopic techniques of injection, clipping, stents, balloons, and Stretta, the endoscope is a valuable adjunct to providing comprehensive care.

Long-term complications of malabsorption may include vitamin deficiency such as vitamin B12, iron, vitamin D, calcium, and folate. Çalapkorur and Küçükkatirci^[4] from Nevsehir, Turkey described each deficiency in detail. This review is a must read for all providers caring for postoperative bariatric surgery patients. Vitamin deficiencies, such as in thiamine, if go unrecognized, can lead to serious and irreversible neurological problems. Early identification and early treatment are crucial.

The sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) are the most commonly performed weight loss operations in the world. Fontan *et al.*^[5] stated they prefer RYGB for patients with gastro-esophageal reflux disease (GERD). However, other procedures such as the one anastomosis gastric bypass (OAGB) have been growing in popularity despite the concern for bile reflux. The Paris Descartes Faculty of Medicine studied reflux, Barrett's esophagus, and esophageal cancer^[6]. They shared their findings and concluded that the OAGB operation appears to be safe in an animal model.

The devil is in the details with any operation. Aktokmakyan *et al.*^[7] from Istanbul, Turkey reviewed the technical steps to a perfect sleeve gastrectomy. They cited the literature including the 5th International Consensus Conference. Their paper includes high resolution intraoperative photographs. While I also use a 36 fr Bougie to size my sleeve, I disagree that the anastomosis must be checked by methylene blue or endoscopy. I also no longer place a drain. Today, many providers utilize an ERAS protocol that limits narcotics and shortens hospital stay.

Fewer than 1% of the patients who meet criteria for weight loss surgery actually have an operation. Aly *et al.*^[8] from Boston Medical Center reviewed psychological, social, and cultural barriers to seeking treatment and getting care.

The Special Issue "Metabolic and Bariatric Surgery" covers the essentials of technique and perioperative care. The Special Issue is also the first to report the use of intra-aortic balloon pump (IABP)^[9] during sleeve gastrectomy and complication of patulous eustachian tube (PET)^[10] after sleeve gastrectomy.

Bariatric surgeons have known for a long time that metabolic operations reverse many comorbid conditions. Society is learning that obesity and related conditions may be life-threatening and metabolic operations lifesaving in the era of COVID-19.

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The author contributed solely to the article.

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Perspective

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Indications and technical details of sublobar resections for small-sized lung cancers based on tumor characteristics

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Abstract

With the recent increase in small-sized lung cancers, sublobar resection and minimally invasive surgeries are becoming preferred. In particular, the detection of ground-glass nodules (GGNs) on high-resolution computed tomography has increased. Although lobectomy has been considered a standard procedure for treating lung cancer, sublobar resections have been indicated for treating GGN-dominant small-sized lung cancers. Wedge resection and segmentectomy have generally been performed as sublobar resection; however, each procedure has some technical advantages and disadvantages. Although anatomical resection as a segmentectomy is a complicated procedure, it has recently been increasingly performed with the accurate anatomical grasp using three-dimensional computed tomography and the identification of the intersegmental plane. Other procedures involving the use of newer technologies can also be performed. Individualized sublobar resection might be a suitable procedure for small-sized lung cancer with the appropriate selection of procedures based on each tumor's characteristics and improving the methods to overcome some technical difficulties.

Keywords: Sublobar resection, ground-glass nodule, wedge resection, segmentectomy, subsegmentectomy, thoracoscopic surgery



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INTRODUCTION

On the basis of a study by Ginsberg *et al.*^[1], it has been considered that lobectomy is the standard procedure for lung cancer treatment. However, more than 20 years have passed since this evidence was reported, and the concept may be inappropriate for small-sized lung cancers in the present era. Recently, the number of detectable small-sized tumors has been increasing owing to the widespread use of computed tomography (CT). It has been reported that prognosis is good if the tumor has a ground-glass opacity (GGO). In their report, Ginsberg *et al.*^[1] did not adequately consider the characteristics of ground-glass nodules. Noguchi *et al.*^[2] reported that wedge resection for small, non-small cell lung cancers (NSCLCs) with GGO has been associated with favorable outcomes.

Moreover, most GGO-dominant lung nodules are adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma, which has a good pathological prognosis^[3,4]. Therefore, the trend of surgical procedures for small-sized GGO-dominant lung nodules has changed from lobectomy to sublobar resection. According to the annual reports from the Japanese Association of Thoracic Surgery, the number of sublobar resections for lung cancer during 2013 to 2017 gradually increased from 23.7% to 27%^[5-9]. Among sublobar resections, wedge resection and anatomical sublobar resections (e.g., segmentectomy) have become widely performed for lung cancers owing to recent technological advancements.

This article aims to describe the indications, methods, problems, and improvements of sublobar resections for small-sized GGO-dominant lung cancers based on the recent literature. We also describe our recent experience with sublobar resections and prospects for future procedures regarding sublobar resections for small-sized lung cancers.

INDICATIONS FOR SUBLOBAR RESECTION

Many reports have compared the use of sublobar resection and lobectomy in small-sized lung cancers, especially those less than 2.0 cm in diameter^[10-13]. A randomized trial for peripheral small-sized lung cancer < 2.0 cm in diameter, with or without GGO components such as CALBG 140503 and JCOG0802/WJOG4607L, is currently in progress, and the superiority of sublobar resections is expected to be proven^[14,15].

The prognosis of small-sized GGO-dominant lung cancers is generally good^[3,4]. Yano *et al.*^[16] reported that patients with small-sized GGO-dominant lung cancers were good candidates for limited wedge resection and segmentectomy. Among tumor characteristics seen on CT, tumor size and GGO ratio are important factors for the indications of sublobar resection. Asamura *et al.*^[4] reported that tumors < 2 cm in diameter with a GGO ratio > 75% on radiography were pathologically non-invasive. Nakata *et al.*^[17] indicated that patients with GGO ratios > 50% should be considered candidates for sublobar resection, although those with a GGO ratio of 50% exhibited vessel infiltration and experienced local recurrence after wedge resection. Recently, Sagawa *et al.*^[18] reported that lung cancer patients with a GGO ratio of > 80% were good candidates for sublobar resection.

On the basis of these reports, we have indicated sublobar resection for indeterminate lung nodules in our institution when tumor characteristics meet the following criteria, to strictly secure oncological outcomes: (1) a tumor size < 2 cm; and (2) a GGO ratio > 80%. Moreover, sublobar resection has also been indicated for patients whose heart and pulmonary functions are compromised to preserve pulmonary function^[19]. In other words, sublobar resection is indicated for the following two types: (1) an intentional curative resection for small-sized GGO-dominant lung cancer; and (2) a palliative resection for compromised patients with whom lobectomy is intolerable due to poor pulmonary function.

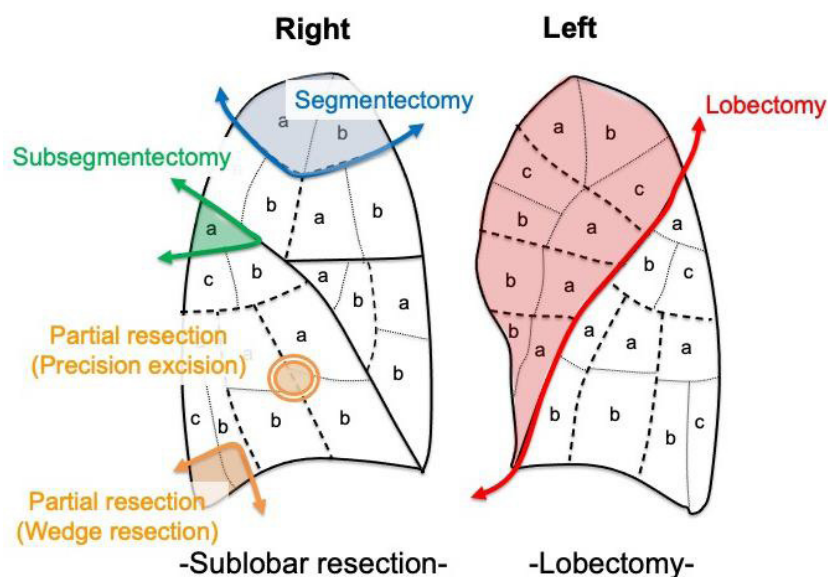


Figure 1. Procedure types for lung cancer. Although lobectomy is a standard procedure, sublobar resections such as segmentectomy, subsegmentectomy, and partial resections have also been performed in the treatment of small-sized lung cancer.

On the other hand, if sublobar resection is acceptable for small-sized lung nodules, a thoracoscopic approach is highly desirable as a minimally invasive surgery. The thoracoscopic approach has better outcomes than thoracotomy in maintaining patients' quality of life and preventing complications. It is preferred over thoracotomy because of its advantages of decreased postoperative pain, shortened chest tube duration, shortened length of hospital stay, faster return to preoperative activity levels, and preserved pulmonary function^[20,21]. Therefore, thoracoscopic sublobar resection is in great demand as a minimally invasive surgical procedure.

TYPES OF SUBLOBAR RESECTIONS AND THE TECHNICAL ASPECTS OF EACH PROCEDURE

Although lobectomy has been traditionally performed as a standard procedure in many patients with lung cancer, sublobar resections have also been performed according to each patient's preoperative condition [Figure 1]. Among sublobar resections, wedge resection and segmentectomy have generally been performed for small-sized lung cancer treatments. Wedge resection has been widely performed to diagnose indeterminate lung nodules or to cure small-sized GGO-dominant lung tumors, as the procedure is not complicated^[22]. Although segmentectomy is generally thought to be more complicated than wedge resection, the oncological outcomes of segmentectomy in a propensity-matched study were comparable to those of lobectomy for patients with early-stage NSCLC^[11]. Therefore, segmentectomy has been advocated as an alternative procedure for lobectomy in recent years^[10].

In addition to wedge resection and segmentectomy, other procedures such as subsegmentectomy have also been performed, although not as commonly as wedge resection and segmentectomy.

Subsegmentectomy is a more minute anatomical procedure than segmentectomy, and it is indicated for smaller GGO-dominant lung cancers in which a sufficient surgical margin can be secured. In this procedure, it is necessary to understand more peripheral anatomical structures^[23]. If the tumor size is small and the GGO component ratio large, and if a sufficient surgical margin can be secured, subsegmentectomy can be accepted as a procedure among sublobar resections because the number of reports on the procedure has increased recently^[24,25]. Another characteristic of subsegmentectomy is that it has the advantage

of securing better surgical margins by segmentectomy combined with adjacent subsegmentectomy if segmentectomy alone cannot secure sufficient surgical margins.

Perelman first described the traditional precision excision method; it is somewhat similar to wedge resection but involves the non-use of some staplers and the use of electrocautery to secure a sufficient surgical margin^[26]. This method has the following advantages: (1) maximum conservation of lung tissue in limited resection for deep-seated lesions; (2) minimal deformity or damage to the adjacent lung tissue; and (3) ability to obtain the maximum margin of tissue around lesions^[27]. A large wedge resection using a stapler might cause a large deformation; in such cases, this method can be advantageous. In particular, when the tumor is superficial on a flat surface, such as interlobar in hilum site or at the bottom of the lower lobe, this method might be useful, as wedge resection using a stapler might be impossible to perform due to a thick parenchyma.

While segmentectomy and subsegmentectomy are anatomical resections, wedge resection and precision excision are non-anatomical resections. There are some advantages and disadvantages to anatomical resections because it is necessary to dissect the hilar area. While lymph node metastasis can be evaluated via lymph node dissection, severe adhesion of the hilum can occur after surgery. Therefore, in cases where cancer recurs and a second surgery is needed after the first surgery, it is assumed that performing a second surgery is difficult due to severe adhesions. On the other hand, although non-anatomical resections have an advantage in that adhesion of the hilum is less likely to occur, it is challenging to evaluate lymph node metastasis. Therefore, non-anatomical resections might be appropriate for cases that do not require evaluation of lymph node metastasis. Thus, there are conflicting differences between anatomical and non-anatomical resections. Careful selection of these procedures must be performed by considering the future clinical course of each patient.

Generally, the decision between anatomical resection as segmentectomy and non-anatomical resection as wedge resection depends on the tumor location in small-sized lung cancer. For example, Doo *et al.*^[28] reported that wedge resection would be difficult for tumors located > 20 mm from the pleural surface. Suzuki *et al.*^[29] suggested that the probability of nodule detection failure is high for tumors located > 5 mm from the pleural surface and for tumors < 10 mm in diameter. In sublobar resection techniques, it is important to secure sufficient surgical margins from targeted tumors^[30]. The surgical margins are assumed to be more limited in wedge resection than in segmentectomy because wedge resection for tumors deeply located from the pleural surface makes it difficult to secure an adequate surgical margin. Mohiuddin *et al.*^[31] reported that the margin distance in wedge resection for small non-small cell carcinoma affects local recurrence and that increasing the margin distance significantly decreases the local recurrence risk. The selection of these procedures should be considered to secure sufficient surgical margins based on tumor characteristics, such as tumor location, size, and depth from the pleural surface. However, the types of sublobar resection remain controversial^[32]. The selection of sublobar resections may differ in each institution because each procedure has its own respective advantages and disadvantages for a precise resection that can secure a sufficient surgical margin.

TECHNICAL PROBLEMS OF SUBLOBAR RESECTIONS

Localization of a small-sized tumor during wedge resection

Although wedge resection is a simple procedure, precise resection of the targeted tumor is challenging when the tumor location is undetectable. For example, when the tumor is located deep within the parenchyma, tumor detection is complicated because these tumors are not easily visualized or palpated by the surgeon's finger under thoracoscopy. Therefore, the localization and identification of small-sized GGO lung tumors during thoracoscopic surgery is challenging, and various methods have been reported^[33-36]. The standard traditional method using a CT-guided hook wire involves the risk of complications such as

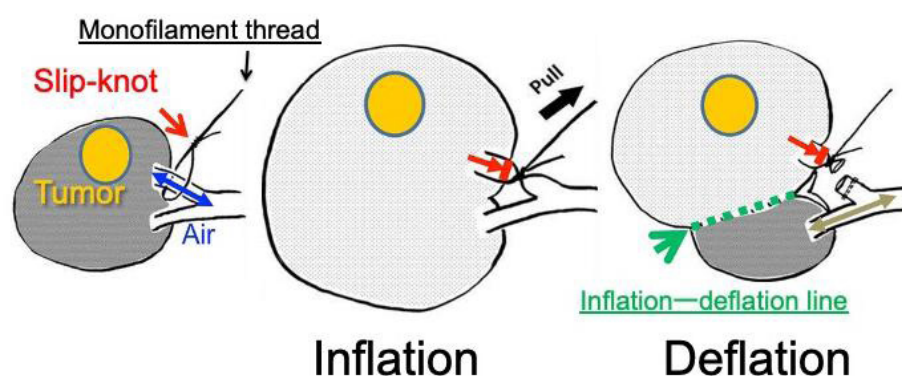


Figure 2. Slip-knot technique. The slip-knot made with a monofilament thread is fully pulled to ligate the targeted segmental bronchus after bilateral lung ventilation. The affected segment remains inflated, while adjacent segments appear collapsed. The targeted segmental bronchus is then divided with a stapler.

pneumothorax, hematoma, and air embolism^[37,38]. Therefore, to avoid these complications, the development of alternative methods has been discussed in recent years.

Identification of intersegmental planes in segmentectomy

In segmentectomy and subsegmentectomy, it is essential to understand the precise anatomy of the patient's bronchus and pulmonary vessels. To precisely understand the anatomic structure of the pulmonary vessels and bronchus, three-dimensional (3D) CT reconstruction is used. There are many reports on the understanding of anatomical structures using a 3D reconstruction tool^[39-41]. The critical process of segmentectomy and subsegmentectomy is ensuring the intersegmental plane and the intersubsegmental plane while dividing the parenchyma along the intersegmental and intersubsegmental lines. Although the inflation-deflation line using jet ventilation is a traditional method used to ensure the intersegmental plane and the intersubsegmental planes^[42], its disadvantages include lack of technical skills for performing bronchoscopy by anesthesiologists, use of jet ventilation, and difficulty in patients with emphysematous lung. Accordingly, other methods for visualizing the intersegmental plane (selective dye injection into the segmental bronchus using a needle) have been reported^[43]. Although this technique may be accessible in open thoracotomy, it is difficult to complete during thoracoscopic surgery. To perform segmentectomy thoracoscopically, we have improved thoracoscopic segmentectomy using the following simplified technique: the slip-knot technique for creating an intersegmental plane [Figure 2]^[44]. The essential device of this technique is simply a slip-knot made by a monofilament thread, and the essential process is merely pulling of the slip-knot. Therefore, this method is simpler, easier, and less expensive than any other conventional method. In our institution, air insufflation through a targeted segmental bronchus incision has recently been performed [Figure 3]. We believe this technique is simple and useful.

RECENT TECHNICAL IMPROVEMENTS IN THORACOSCOPIC SUBLOBAR RESECTIONS

Localization methods for small-sized tumors in wedge resection

In the localization method of wedge resection for targeted tumors, Gill *et al.*^[45] conducted a prospective clinical trial of image-guided video-assisted thoracoscopic surgery (iVATS), in which percutaneous markings are created with two T-bars utilizing intraoperative C-arm CT. In this study, the targeted tumor was successfully resected with no intraoperative complications. In recent years, the number of iVATS methods has increased due to the introduction of C-arm CT in many institutions^[46,47]. This method, which is advantageous without serious complications, was also introduced to our institution. Moreover, the most recent technology is the marking method in which the area near the tumor is marked using a wireless marking system (The radiofrequency identification system, Hogy Medical Co, Ltd, Tokyo, Japan)^[48]. This method is a transbronchial approach using bronchoscopy and can reduce complications such as air

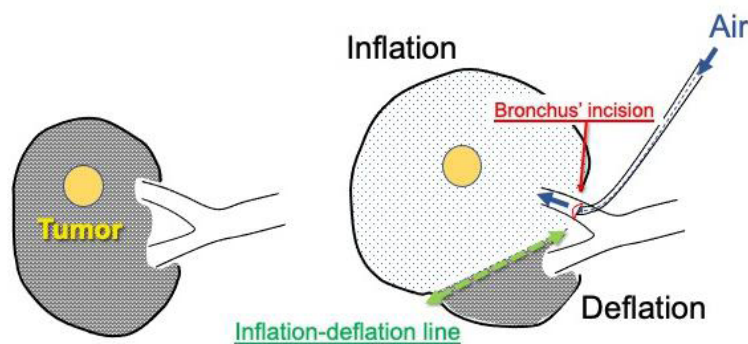


Figure 3. The targeted segmental bronchus incision is made to inflate the affected segment by air insufflation.

embolism by avoiding parenchymal puncture. Although these methods depend on the equipment of every institution, it is expected that an iVATS method or a wireless marking system will become a significant method of tumor identification in the future.

Identification methods for intersegmental planes in segmentectomy

For visualization and division of the intersegmental plane in segmentectomy, a new thoracoscopy detection method involving the use of indocyanine green has become increasingly popular^[49-51]. Furthermore, Sato *et al.*^[52] reported that the VAL-MAP method, which can secure sufficient surgical margins using the dye around the tumor before segmentectomy, has been growing increasingly popular in Japan. Regarding the 3D reconstruction of pulmonary vessels and the bronchus, there is an improvement in 3D-CT and anatomical reconstruction progression in 3D models' references using 3D printers^[53]. These improvements have assisted in the performance of various types of thoracoscopic segmentectomies.

THORACOSCOPIC SUBLOBAR RESECTIONS BASED ON INDICATION CRITERIA FROM OUR INSTITUTION AND PROSPECTS FOR SUBLOBAR RESECTION

Based on the above description, we performed sublobar resections for patients who meet the following criteria: (1) non-solid lung tumor with planned resection of a cT1aN0M0 primary lung cancer, < 2 cm in diameter, with a GGO ratio > 80%, as determined by high-resolution CT in patients with good pulmonary function and who can tolerate lobectomy; and (2) limited cardiopulmonary reserve or organ failure in compromised patients who are considered poor candidates for lobectomy. Regarding the approach, thoracoscopic sublobar resection was indicated whenever we thought it was possible. Our thoracoscopic surgical strategy for small-sized lung nodules is shown in Figure 4.

In September 2015, we introduced a hook wire method under general anesthesia using C-arm CT to avoid complications such as air embolism [Figure 5A and B]. To prevent air embolism, CT-guided lung biopsy under breath-holding and hook wire localization after exhalation has been reported because negative intrathoracic pressure is assumed to be associated with atmospheric air aspiration into the pulmonary vasculature^[54-56]. We applied the hook wire method based on the assumption that air embolism might occur under spontaneous breathing but not at the end of the exhalation phase because it is assumed that breath-holding might be easier to manage under general anesthesia. We performed wedge resection using this method in 16 cases; serious complications such as air embolism did not occur during the procedure. The precision excision method has been performed in approximately 20 cases since 2009 [Figure 6A-C]. In this method, we used an energy device to divide the parenchyma in addition to electrocautery, and the energy device was useful in the control of bleeding and air leakage during the surgery. This method was indicated for cases in which tumor resection using a stapler was expected to be inappropriate due to the tumor's

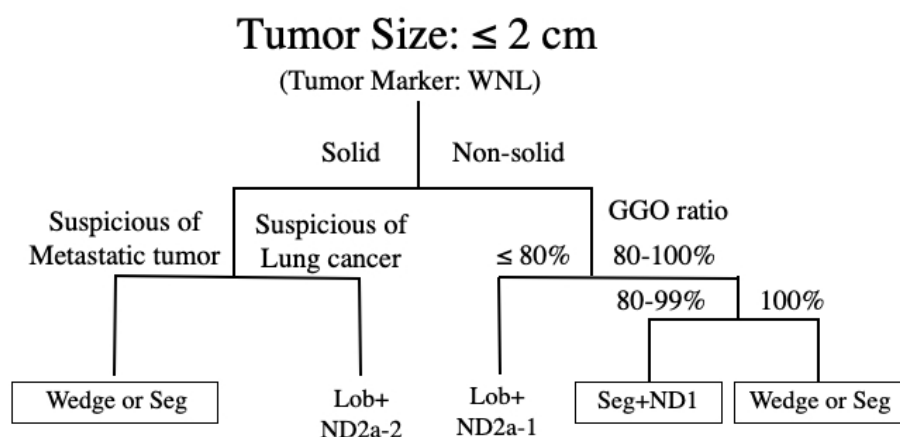


Figure 4. Thoracoscopic surgical strategy for a small-sized lung tumor in our institute. WNL: Within normal limit; GGO: ground-glass opacity; Wedge: wedge resection; Lob: lobectomy; Seg: segmentectomy; ND: nodal dissection.



Figure 5. Current tumor marking method: A hook wire placement is performed under general anesthesia in a hybrid operating room. After the patient was intubated with a double-lumen tube under general anesthesia, the targeted tumor was identified using C-arm CT (A). A hook wire was then inserted near the targeted tumor, referring to the CT image (B). After tumor marking, the targeted tumor was resected via wedge resection.

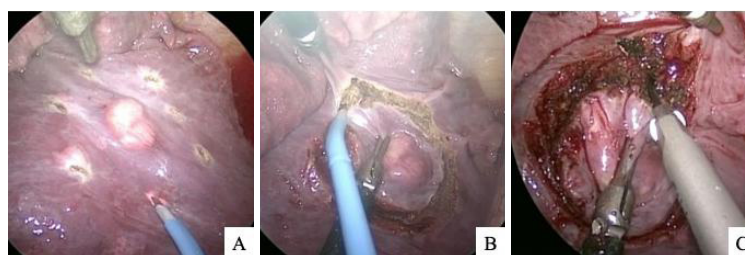


Figure 6. Precision excision method for small-sized tumors. First, some markings were performed around the targeted tumor using electrocautery (A). Second, the visceral parenchyma was divided with a sufficient surgical margin using electrocautery (B). Finally, the parenchyma was divided using an energy device, and the targeted tumor was resected (C).

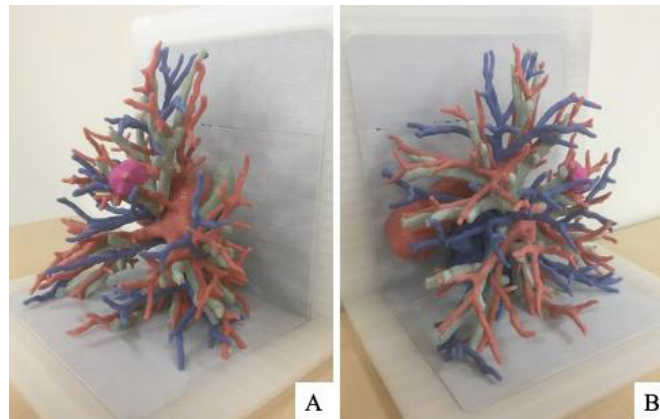


Figure 7. A three-dimensional model of the pulmonary vessels and bronchus was made using a three-dimensional printer. The pink color represents the targeted tumor, the white color represents the bronchi, the red color represents the pulmonary arteries, and the blue color represents the pulmonary veins.

location. The surgical margins were sufficiently secured, and there were no recurrences.

Recently, we introduced a wireless marking method for the treatment of indeterminate lung nodules^[48]. Three patients underwent wedge resection after marking. In all cases, the tumors were completely resected, and one patient was diagnosed with AIS. Although the number of cases is still small, we believe that these methods are useful for tumor identification in wedge resection.

From July 2004 to August 2020, thoracoscopic segmentectomy and subsegmentectomy for lung cancer were performed using 3D-CT simulation in 366 patients. Segmentectomy was done in 247 cases, subsegmentectomy in 69 cases, and segmentectomy combined with adjacent subsegmentectomy in 50 cases. We applied 3D-CT simulation and the slip-knot technique for these anatomical sublobar resections. First, the parenchyma was dissected using an energy device from the hilar site to the peripheral site along the intersegmental veins. Following the division of the segmental artery and vein, the segmental bronchus was dissected, and an inflation-deflation line was created^[44]. The inflation-deflation line can be gradually identified as the intersegmental line. The bronchus was then divided with a stapler or ligated with a silk thread based on the bronchial diameter. The parenchyma was then dissected along the intersegmental veins and the inflation-deflation lines using either an electrocautery or an energy device, and the venous branches running into the affected segment were divided. Finally, the peripheral parenchyma was divided using a stapler. With these techniques, our thoracoscopic segmentectomy and subsegmentectomy procedures secured sufficient surgical margins and were thoroughly improved. The outcomes of thoracoscopic segmentectomy and subsegmentectomy were excellent, and there were no recurrences in intentional cases on the basis of our criteria of sublobar resections, although a small number of compromised cases were known to have recurrences. Thus, we performed thoracoscopic sublobar resections for small-sized lung cancers using these methods, and the outcomes were satisfactory in terms of curative operation. Although we have mainly indicated sublobar resection in GGO-dominant tumors, this procedure might also be indicated in small-sized solid tumors less than 2.0 cm in diameter because previous studies have reported favorable outcomes^[10-15].

In recent years, we have referred to a 3D model of the pulmonary vessels and bronchus before and during surgery [Figure 7A and B]. The model is useful for understanding the precise anatomy of each patient. We prepared this model mainly for anatomical sublobar resections in patients with whom tumor localization is expected to be difficult. Moreover, reports on the single-port approach have been increasing. We also began various types of segmentectomies using this approach and investigated its safety and feasibility.

Furthermore, minimally invasive surgery has progressed in robotic surgery. Robotic surgery is more suitable for small spaces, such as the pelvic cavity. A small working space is sufficient to perform sublobar resections. A new style robot system such as a da Vinci SP may be effectively used for sublobar resections as a minimally invasive surgical procedure in the future.

The selection of procedures for sublobar resection must be adapted to each patient according to tumor size, GGO ratio, and tumor location. Individualized sublobar resection will continue to evolve with applications such as CT and other new methods.

In conclusion, thoracoscopic sublobar resection might be a suitable procedure for small-sized lung cancers with the appropriate selection of procedures based on each tumor's characteristics and methods described herein and will continue to be further improved with new technologies in the future.

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Authors' contributions

Substantial contributions to the conception and design of the study: Kato H, Oizumi H, Suzuki J, Suzuki K, Takamori 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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Original Article

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Comparative analysis of perioperative outcomes between robot-assisted partial nephrectomy and open partial nephrectomy: a propensity-matched study

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Abstract

Aim: Partial nephrectomy is the standard treatment for small renal tumors; however, it remains unclear which surgical approach from among robot-assisted partial nephrectomy (RAPN) and open partial nephrectomy (OPN) is superior. This study aimed to compare perioperative outcomes of RAPN and OPN performed at a single institution after adjusting for preoperative patient and tumor characteristics using propensity score matching (PSM).

Methods: In this retrospective cohort study, patients who underwent RAPN or OPN for a renal mass of cT1-2 N0 M0 between 2005 and 2020 at our institution were recruited. The study outcomes were perioperative outcomes, complications, and pathological and functional outcomes. PSM was used to account for baseline covariates.

Results: Overall, 131 RAPN and 71 OPN cases were extracted; in addition, 58 cases of RAPN and OPN were selected via PSM. RAPN was superior to OPN in terms of estimated blood loss (10 g vs. 160 g, $P < 0.001$), ischemia time (23 min vs. 34 min, $P < 0.001$), and hospital duration (7 days vs. 12 days, $P < 0.001$). There were no significant differences in the incidence of perioperative complications or in the rate of positive surgical margins (both $P > 0.05$). With respect to functional outcomes, the rates of preservation of renal function at both 1 day and 3 months postoperatively were higher with RAPN than with OPN (85.3% vs. 69.1% and 93.3% vs. 85.6% respectively, both $P < 0.001$).



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Conclusion: In selected cases, RAPN with warm ischemia appears to preserve renal function equally well or better compared to OPN with cold ischemia.

Keywords: Partial nephrectomy, robot-assisted nephrectomy, open surgery, perioperative outcomes, renal function, propensity score matching

INTRODUCTION

Partial nephrectomy (PN) for localized renal cell carcinoma has been reported to have oncological outcomes equivalent to those achieved by radical nephrectomy, with preservation of postoperative renal function^[1,2]. As a result, PN has become the standard treatment for small renal cell carcinomas.

Robot-assisted partial nephrectomy (RAPN) is recognized as a minimally invasive surgical method. Its application as an alternative to open partial nephrectomy (OPN) is rapidly growing^[3,4]. This is largely due to RAPN's high-definition 3D optical system and flexible wristed instruments that allow surgeons to perform tumor excision and renorrhaphy with an accuracy equal to or greater than that achieved by OPN^[5].

Various studies have compared RAPN and OPN^[6-12]. However, because the outcomes of PN are influenced by several factors, including tumor location, anatomical complexity, patient renal function, and operator proficiency, there is some controversy over which surgical approach is superior. Current guidelines do not indicate a preference for one technique over the other, leading to decisions being predominantly made on the basis of the surgeons' expertise and skills^[13].

The present study aimed to comprehensively compare the perioperative outcomes of RAPN and OPN performed at a single institution after adjusting for preoperative patient and tumor characteristics using propensity score matching (PSM).

METHODS

Study population

This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R1581).

We retrospectively collected clinical data of 202 patients with renal masses of cT1-2 cN0 cM0 diagnosed via CT or MRI who underwent RAPN or OPN between 2005 and 2020 at Kyoto University Hospital. During this period, RAPN was performed by 10 experienced surgeons and OPN was performed by 15 experienced surgeons. The choice of the surgical method (RAPN or OPN) was determined on a case-by-case basis at a preoperative medical conference. However, due to insurance coverage changes that came into effect in 2016, RAPN became the preferred technique. As a general rule, OPN has been applied to patients with a single kidney or chronic kidney disease (CKD) grade 4 or higher (eGFR < 30) since 2016. Cases where preoperative imaging was not available were excluded from the study because the anatomic complexity of the tumors could not be accurately determined. Cases with multiple tumors were also excluded for the same reason. Cases in which other surgeries were simultaneously conducted with PN were excluded because perioperative outcomes of PN surgery could not be accurately evaluated.

Surgical technique

The surgeons at our hospital have received adequate surgical training, have performed many operations at our hospital and other institutions, and are qualified practitioners in Japan. The RAPN procedure employed at our hospital was relatively similar to that reported by Kaouk *et al.*^[14] and was performed using the da

Vinci S or Xi surgical system (Intuitive, CA, USA). In many cases, the renal artery was clamped using a bulldog clamp. However, when the tumor was superficial and peripheral, the zero ischemia technique was performed, in which the renal artery was not clamped^[15]. The tumor was then resected along its outline, as confirmed by ultrasonography beforehand. The resection margin was 3-5 mm. If the renal pelvis was open, a central suture was performed to ensure that there was no urine leak before renorrhaphy. The renal artery was declamped after renorrhaphy to check for bleeding from the cut surface.

OPN was performed using the subcostal or flank approach. In most cases, the retroperitoneal approach was used, and OPN under cold ischemia was performed. The renal artery was clamped, and the entire kidney was surrounded by ice slush for 5-10 min before tumor resection^[16]. Open calyces and bleeding sites were carefully repaired and renorrhaphy was performed. The renal artery was declamped after renorrhaphy.

Outcomes of interest

The primary and secondary outcomes were examined and compared as evaluation points between RAPN and OPN.

The primary outcomes were perioperative outcomes, namely estimated blood loss (EBL), operative time, ischemia time, and hospital stay. All intraoperative and postoperative complications were also evaluated based on the Clavien-Dindo (CD) classification^[17].

The secondary outcomes were pathological and functional outcomes, namely the rates of malignancy, positive surgical margins in malignancy, and pathological stage. Renal function was measured at baseline and at 1 day and 3 months postoperatively based on the estimated glomerular filtration rate (eGFR). The ratio of eGFR at both 1 day and 3 months postoperatively to the baseline eGFR (% preservation of eGFR) was used as an index to evaluate the postoperative residual renal function.

Covariates

Patients' preoperative variables were analyzed as covariates, including age at treatment, sex, body mass index (BMI), Charlson comorbidity index (CCI)^[18], preoperative eGFR, clinical stage, clinical tumor size (the maximum diameter at preoperative imaging), and tumor side (left or right). Tumor complexity and anatomical characteristics were determined by the urologist and defined using the total "RENAL" nephrometry score^[19], namely Radius (tumor size as maximal diameter), Exophytic/endophytic properties of the tumor, Nearness of tumor's deepest portion to the collecting system or sinus, Anterior/posterior descriptor, and the Location relative to the polar line.

Statistical analyses

Statistical analyses and interpretation of the results were performed according to established guidelines^[20]. Continuous variables are presented as median and interquartile range (IQR) or mean and standard deviation. Categorical variables are presented as frequency and proportion. Differences in the distribution of continuous and categorical variables between the RAPN and OPN groups were compared using the Mann-Whitney and chi-square tests, respectively.

Adjustments were made using 1:1 nearest-neighbor PSM to account for possible baseline differences between patients who underwent OPN and RAPN^[21]. Propensity scores were calculated using a logistic regression model with odds of receiving RAPN as a dependent variable and age at treatment, sex, BMI, CCI, preoperative eGFR, clinical stage, clinical tumor size, tumor side (right or left), individual RENAL score item, and total RENAL nephrometry score as independent variables. After balanced matching of covariates, the effects of the surgical procedures on outcomes were estimated using the Mann-Whitney and chi-square tests for continuous and categorical variables, respectively.

All statistical tests were performed using JMP Pro 15.1.0. For all statistical analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

As shown in [Table 1](#), a total of 202 patients (131 RAPN and 71 OPN) were included in this study. Prior to PSM, the patients in the cohort who underwent RAPN had a significantly higher BMI ($P = 0.006$) than those who underwent OPN. Furthermore, they had significantly lower RENAL nephrometry scores than those who underwent OPN (6.8 ± 1.61 vs. 7.5 ± 1.56 , respectively; $P = 0.003$). A total of 116 cases were compared, comprising 58 RAPN cases and 58 OPN cases that were matched by PSM. In the post-PSM cohort, there were no differences between the RAPN and OPN groups for any of the covariates assessed (all $P > 0.05$) [[Figure 1](#)].

Perioperative outcomes and complications

EBL was significantly higher and hospital stay longer in the OPN group than in the RAPN group [[Table 2](#)]. Ischemia time was significantly longer in the OPN group than in the RAPN group; however, cold ischemia time accounted for the majority of the ischemia time in the OPN group.

There were no intraoperative complications in any of the 116 cases selected by PSM. However, postoperative complications occurred in 11 patients who underwent OPN and 8 patients who underwent RAPN.

In both patients who underwent RAPN and OPN, postoperative complications of CD grade 3 or higher included urinomas requiring ureteral stenting and pseudoaneurysms requiring embolization. There was no significant difference in the incidence of postoperative complications between OPN and RAPN [[Table 2](#)].

Pathological outcomes

After PSM, one case of pT2a and one case of pT3a were observed in patients who underwent OPN. There was no difference between the OPN and RAPN groups in terms of positive surgical margins [[Table 3](#)].

Functional outcomes

In the post-PSM cohort, the % preservation of eGFR at both 1 day and 3 months postoperatively was significantly better in the RAPN group than in the OPN group, although the eGFR at 3 months was not significantly different between the two groups. There were fewer cases with upstaged CKD grades in the RAPN group than in the OPN group (30 cases with OPN vs. 17 cases with RAPN; $P = 0.014$) [[Table 3](#)]. The changes in eGFR for all cases, imperative cases, and elective cases are shown in [Figure 2](#).

Multivariate analysis

In the pre-PSM cohort, RAPN was found to be a good predictor of EBL ($P < 0.0001$), ischemia time ($P < 0.0001$), transfusion rate ($P = 0.019$), hospital stay ($P < 0.0001$), eGFR ($P < 0.0001$) and % preservation of eGFR ($P < 0.0001$) at the 3rd postoperative month (POM), and CKD upstaging ($P = 0.001$) via multivariate analysis [[Figure 3](#)].

DISCUSSION

Previous studies have shown mixed results when comparing the outcomes of RAPN and OPN. Simhan *et al.*^[11] compared perioperative outcomes of 281 patients with moderately and highly complex renal lesions. The results showed that RAPN yielded perioperative and functional outcomes similar to OPN, with the additional benefit of shorter hospital stays. Garisto *et al.*^[6] compared perioperative, functional, and

Table 1. Descriptive characteristics of the study population and tumor characteristics

Variables	Cohort before PSM			Cohort after PSM			SMD
	OPN (n = 71)	RAPN (n = 131)	P value	OPN (n = 58)	RAPN (n = 58)	P value	
Age (yr)			0.065			0.36	0.173
Mean (SD)	59.4 (14.1)	63.0 (12.7)		59.3 (13.4)	61.7 (14.3)		
Sex, n (%)			0.56			0.83	
Male	51 (71.8)	99 (75.6)		43 (74.1)	44 (75.9)		
Female	20 (28.2)	32 (24.4)		15 (25.9)	14 (24.1)		
BMI, kg/m ²			0.006			0.78	0.052
Mean (SD)	23.2 (4.1)	24.8 (3.8)		23.8 (4.2)	23.6 (3.5)		
Charlson comorbidity index, n (%)			0.36			0.90	
0	35 (49.3)	76 (58.0)		30 (51.7)	29 (50.0)		
1	11 (15.5)	28 (21.4)		11 (19.0)	11 (19.0)		
2	19 (26.8)	20 (15.3)		15 (25.9)	14 (24.1)		
≥ 3	6 (8.4)	7 (5.3)		2 (3.4)	4 (6.9)		
eGFR (mL/min/1.73 m ²)			0.35			0.51	0.275
Median (IQR)	64.1 (45.1-86.0)	66.3 (56.6-77.0)		64.7 (47.1-86.0)	62.1 (54.9-73.3)		
Imperative case, n (%)	34 (47.9)	44 (33.6)	0.046	24 (41.3)	25 (43.1)	0.85	
Clinical stage, n (%)			0.19			1.00	
cT1a	55 (77.5)	111 (84.7)		49 (84.5)	49 (84.5)		
cT1b	13 (18.3)	20 (15.3)		9 (15.5)	9 (15.5)		
cT2a-b	2 (2.8)	0 (0)		0 (0)	0 (0)		
Tumor size (cm)			0.26			0.63	0.089
Median	3.0	2.7		2.5	3.0		
IQR	2.1-3.9	2.0-3.5		1.8-3.6	2.0-3.7		
Tumor side, n (%)			0.45			1.00	
Left	37 (52.1)	61 (46.6)		28 (48.3)	28 (48.3)		
Right	34 (47.9)	70 (53.4)		30 (51.7)	30 (51.7)		
RENAL nephrometry score			0.08			0.80	
Radius, n (%)							
≤ 4 cm	54 (76.1)	111 (84.7)		49 (84.5)	48 (82.8)		
4-7 cm	15 (21.1)	20 (15.3)		9 (15.5)	10 (17.2)		
≥ 7 cm	2 (2.8)	0 (0)		0 (0)	0 (0)		
Exophytic/endophytic			0.17			0.71	
≥ 50% Exophytic	25 (35.2)	53 (40.5)		20 (34.5)	23 (39.7)		
< 50% Exophytic	33 (46.5)	66 (50.4)		27 (46.6)	27 (46.4)		
Endophytic	13 (18.3)	12 (9.1)		11 (19.0)	8 (13.8)		
Nearness to the collecting system			0.25			0.90	
≥ 7 mm	15 (21.1)	42 (32.1)		14 (24.1)	12 (20.7)		
4-7 mm	16 (22.5)	24 (19.8)		11 (19.0)	11 (19.0)		
≤ 7 mm	40 (56.3)	65 (49.6)		33 (56.9)	35 (60.3)		
Anterior/posterior, n (%)			0.52			0.23	
Anterior	37 (52.1)	60 (45.8)		30 (51.2)	28 (26)		
Posterior	29 (40.9)	56 (42.3)		24 (41.4)	31 (53.5)		
Location relative to the polar lines			0.02			1.00	
Above or below the polar line	16 (22.5)	56 (42.8)		16 (27.6)	16 (27.6)		
Lesion crosses the polar line	33 (46.5)	44 (33.6)		23 (39.7)	23 (39.7)		
> 50% is across the polar line and crosses the axial midline entirely between the polar lines	22 (31.0)	31 (23.7)		19 (32.8)	19 (32.8)		
Total score, mean (SD)	7.5 (1.56)	6.8 (1.61)	0.003	7.4 (1.58)	7.4 (1.51)	0.95	0

RAPN: Robot-assisted partial nephrectomy; OPN: open partial nephrectomy; PSM: propensity score matching; eGFR: estimated glomerular filtration rate; SD: standard deviation; IQR: interquartile range; SMD: standardized mean difference; Imperative case: single kidney, bilateral tumors, or chronic kidney disease (eGFR < 60).

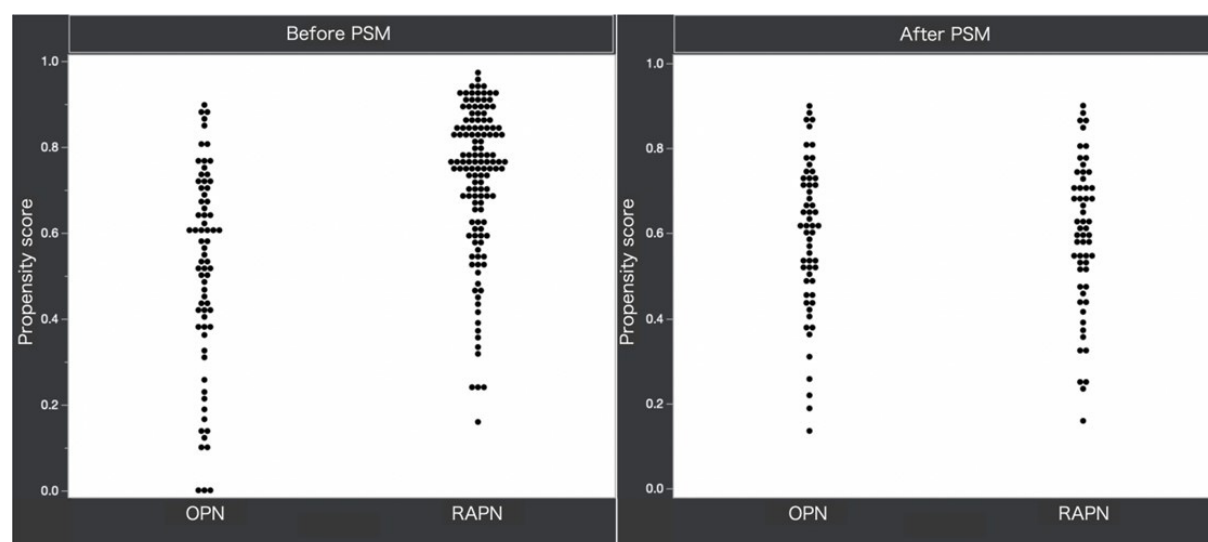


Figure 1. Distribution of the propensity scores. Before PSM (left) and after PSM (right). PSM: propensity score matching; OPN: open partial nephrectomy; RAPN: robot-assisted partial nephrectomy.

Table 2. Comparison of perioperative outcomes between patients treated with RAPN and those treated with OPN after propensity score matching for clinical characteristics

Variables	OPN (n = 58)	RAPN (n = 58)	P value
EBL (mL)			< 0.001
Median (IQR)	160 (90-300)	10 (0-60)	
Operative time (min)			0.003
Median (IQR)	232 (200-260)	258 (223-297)	
Renal artery clamping, n (%)			0.31
Main artery clamping	55 (94.8)	57 (98.3)	
Zero ischemia	3 (5.2)	1 (1.7)	
Ischemia time (min)			< 0.001
Median (IQR)	34 (26-44)	23 (18-28)	
Cold ischemia time	27 (21-36)	0	
Transfusion, n (%) (including autologous blood transfusions)	4 (6.9)	1 (1.7)	0.17
Hospital stay, days			< 0.001
Median (IQR)	12 (9-14)	7 (7-9)	
Conversion to radical nephrectomy, n (%)	2 (3.5)	2 (3.5)	1.0
Overall postoperative complications, n (%)	11 (19.0)	8 (13.8)	0.64
Clavien-Dindo complication ≤ 2	8 (13.8)	3 (5.2)	0.11
Clavien-Dindo complication ≥ 3	3 (5.2)	5 (8.6)	0.46

EBL: estimated blood losses; IQR: interquartile range; OPN: open partial nephrectomy; RAPN: robot-assisted partial nephrectomy.

oncological outcomes of RAPN and OPN for the treatment of highly complex renal tumors of 279 cases. Their results indicated that RAPN presents a safe and effective alternative to OPN for highly complex renal tumors, with advantages of reduced blood loss, shorter ischemia time, and shorter length of hospital stay. Other original studies comparing RAPN with OPN have reported that the advantages of RAPN include lower rates of complications^[8,22-24]. Although, there are many retrospective studies comparing OPN and RAPN, few have compared these surgical approaches in a single-institutional setting using PSM. Because our study analyzed RAPN and OPN from a single institution and matched the patients' backgrounds and tumor complexities using PSM, we believe that our results provide a higher level of evidence. In fact, the use of PSM for all preoperative factors, including the RENAL score, in both groups, which are thought to play important roles in determining the indications and outcomes of RAPN and OPN, resulted in no significant differences between the two groups.

Table 3. Pathological and functional outcomes

Variables	OPN (n = 58)	RAPN (n = 58)	P value
Pathological outcomes			
Malignancy, n (%)	55 (94.8)	52 (89.7)	0.30
Positive surgical margins, n (%)	0/55 (0)	1/52 (1.9)	0.50
Stage at final pathology			0.30
pT1a	50 (86.2)	45 (77.6)	
pT1b	3 (5.2)	6 (10.3)	
pT2a-b	1 (1.7)	0 (0)	
pT3a	1 (1.7)	0 (0)	
uncertain	3 (5.2)	7 (12.1)	
Functional outcomes			
eGFR at POD 1, mL/min/1.73 m ²			
Median (IQR)	44.4 (32.3-64.1)	53.1 (40.8-66.6)	0.047
% preservation of eGFR at POD 1 compared with baseline, (%)	69.1 (40.8-66.6)	85.3 (72.0-95.4)	< 0.001
eGFR at 3rd POM, mL/min/1.73 m ²			
Median (IQR)	56.5 (41.9-72.7)	58.3 (48.9-72.0)	0.19
% preservation of eGFR at 3rd POM compared with baseline, (%)	85.6 (78.6-88.6)	93.3 (83.4-100.9)	< 0.001
CKD upstaging at 3rd POM, n (%)	30 (51.7)	17 (29.3)	0.014

RAPN: Robot-assisted partial nephrectomy; OPN: open partial nephrectomy; eGFR: estimated glomerular filtration rate; IQR: interquartile range; POD: postoperative day; POM: postoperative month; CKD: chronic kidney disease.

The results of our study indicate that RAPN is superior to OPN in terms of EBL, ischemia time, and length of hospital stay. In OPN, cases with long ischemia time of more than 40 min were observed, which were caused by difficulty in suturing and hemostasis owing to difficulty in visualizing the site of the opening of the renal pelvis and bleeding point. We found no significant differences in the incidence of perioperative complications or in the rate of positive surgical margins. With respect to functional outcomes, the rates of preservation of renal function at both 1 day and 3 months postoperatively were higher and the rates of CKD grade upstaging were lower for patients who underwent RAPN than for those who underwent OPN.

There are two possible explanations for the higher rate of preserved renal function in patients who underwent RAPN. One is the difference in the volume of nephron loss during PN. The high-definition 3D optical system and flexible wristed instruments used in RAPN result in lower levels of nephron loss in the resection margin compared with OPN. However, this is merely a predictive interpretation because it is not possible to retrospectively and accurately measure the safety margin in all cases.

Another explanation is the difference in the length of ischemia time. It is known that cold ischemia suppresses damage to the remaining kidney even after 30 min^[25,26]. However, although there is clear evidence regarding the protective role of renal cooling in the context of impaired renal function, some studies have suggested that prolonged cold ischemia times and short warm ischemia times also cause nephron damage^[27,28]. Considering the results of this study, even when cold ischemia using ice slush was performed, it appears that if the ischemia time becomes longer, a shorter period of warm ischemia may be more advantageous for preserving renal function than a longer period of cold ischemia. A previous retrospective study found similar results; the OPN group with cold ischemia had a longer ischemia time, and no significant eGFR advantage was found in favor of OPN. In addition, the trend toward GFR recovery was better in the RAPN group, although it did not reach statistical significance^[6].

In studies comparing the effects of cold and warm ischemia and ischemia time on renal function, results showed that when ischemia lasted for 30 min or longer, renal function was better preserved with cold ischemia. This is because cold ischemia reduces the diffuse and irreversible damage to parenchyma

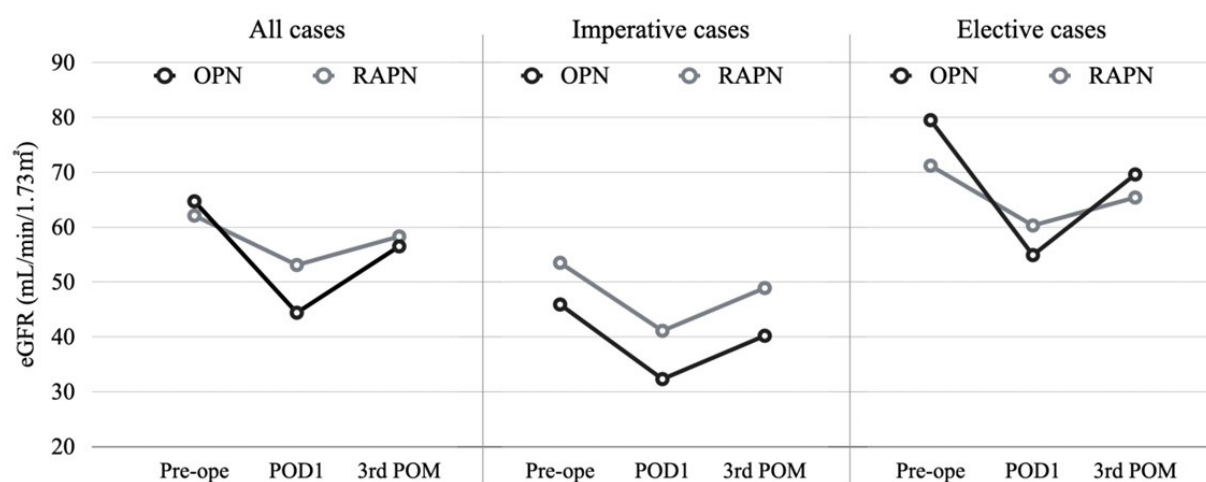


Figure 2. Pre- and post-operative changes in median eGFR in OPN and RAPN for all, imperative, and elective cases. eGFR: Estimated glomerular filtration rate; OPN: open partial nephrectomy; RAPN: robot-assisted partial nephrectomy; Imperative case: single kidney, bilateral tumors, or chronic kidney disease (eGFR < 60).

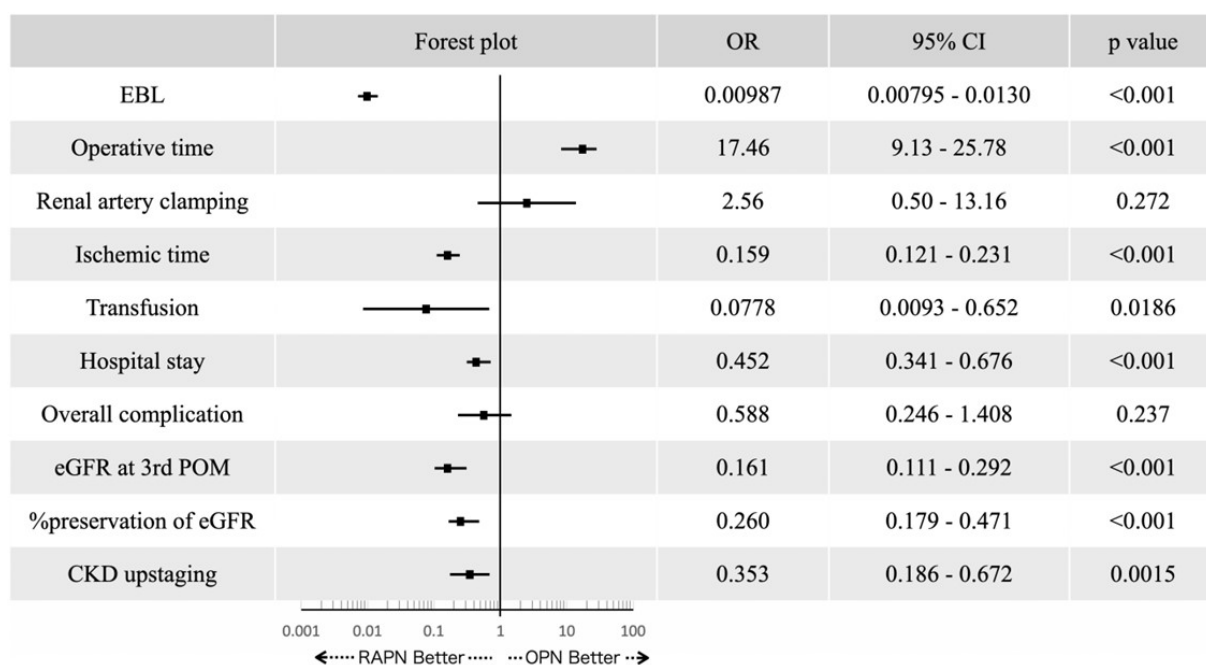


Figure 3. Multivariate logistic regression tests the impact of RAPN vs. OPN on each perioperative outcome according to each OPN and RPN group before matching.

caused by prolonged warm ischemia^[29-35]. However, when ischemia time was less than 20 min, the preservation of renal function was excellent and no significant difference was observed between cold and warm ischemia^[25-28]. In light of our results, even in cases where renal function preservation is strongly desired, RAPN with warm ischemia presents a good option if ischemia time is expected to be short. This is evidenced by the equal or greater postoperative renal function achieved with RAPN over OPN. Furthermore, RAPN seems to have some advantages over OPN in terms of other perioperative outcomes. In fact, a study comparing RAPN and OPN for patients with a solitary kidney also concluded that RAPN may offer comparable perioperative and short-term functional outcomes compared with OPN, assuming careful patient selection and adequate surgical experience^[36].

In contrast, cold ischemia should be selected in cases where the tumor is anatomically complex and when the ischemia time is expected to be prolonged. The shorter the cold ischemia period, the better the postoperative renal function is. Considering this, OPN should be prioritized when it can ensure a faster and more accurate resection and renorrhaphy in cases with complex tumors.

In this study, 73 cases in RAPN and 13 cases in OPN were excluded by PSM. Excluded cases included patients in the RAPN group who were relatively older and had a higher BMI and lower RENAL score, and those in the OPN group who were relatively younger and had larger tumor diameters. Therefore, the results of this study may not necessarily apply to such excluded cases.

In recent years, there has been an increasing number of reports confirming that RAPN can be safely used for the resection of complex or large tumors^[6,37-39]. In this study and other reports, RAPN was shown to have equivalent or better outcomes compared with OPN in many aspects of the perioperative results. This suggests that RAPN is a viable surgical option for the resection of complex and large tumors in the future. However, this hypothesis is based on the premise that the surgeon has sufficient technical proficiency in robotic surgery. Therefore, it is necessary to select an appropriate surgical method according to the surgeon's and the institution's level of proficiency in robotic surgery, taking into consideration the complexity of the tumor and patient factors.

This study had several limitations. First, the sample size of the study was relatively small. Furthermore, it was nonrandomized and retrospective in nature; thus, it was subject to the inherent limitations of a retrospective analysis of observational data, possibly making it difficult to obtain original results. Second, the results of the PSM in this study may be generalized only among those within the propensity score range included in the paired analysis and may not be applicable to those outside this range. Third, different surgeons were involved in this study, which might be seen as a source of biases because different phases of different learning curves were included and might have influenced the results. Fourth, the timing of the surgery (i.e., pre- or post- 2016) was another limitation because more recent cases underwent RAPN and older cases predominantly underwent OPN, as RAPN has been covered by insurance in Japan since 2016. Finally, this study used data collected from a single center with a high incidence of kidney cancer and cannot be generalized to providers with different characteristics.

In conclusion, this study compares the perioperative outcomes of RAPN and OPN performed at a single institution. Our results indicate that RAPN with warm ischemia preserves renal function equally well or better than does OPN with cold ischemia in selected cases with short ischemic times.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Sawada A

Performed data acquisition as well as provided administrative, technical, and material support: Takahashi T, Kono J, Masui K, Sato T, Sano T, Goto T

Drafted the article or revised it for critically important intellectual content and approved the final version: Kobayashi T, Akamatsu S, Ogawa O

Availability of data and materials

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (reference number: R1581).

Consent for publication

Not applicable.

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Editorial

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Neuroimaging in meningiomas: old tips and new tricks

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Abstract

Meningiomas are the most common neoplasm of the central nervous system. Usually benign and generally discovered incidentally at imaging, meningiomas can also be responsible for severe neurological symptoms and deficits, with potentially high morbidity and non-negligible mortality. Therefore, neuroimaging plays a crucial role in meningiomas diagnosis, therapeutic planning, and long-term surveillance, for early detection of both recurrence in treated patients and disease progression in untreated ones. Here, we review conventional findings in meningiomas' imaging, review the role for advanced diagnostic techniques, and offer an overview on possible future neuroimaging applications.

Keywords: Meningioma, magnetic resonance imaging, computed tomography, central nervous system

INTRODUCTION

Meningiomas account for about 36% of all intra-cranial neoplasms, thus representing the most common primary tumor of the central nervous system (CNS)^[1]. They take origin from meningeal membranes covering brain, nerves, and spinal cord, arising from arachnoid mater formed by the cells within middle meningeal layer; therefore, this type of neoplasm, although more common in intra-cranial space, can be found all over the neuroaxis [Figure 1]^[2,3]. More frequent in elderly (peak incidence in 6th-7th



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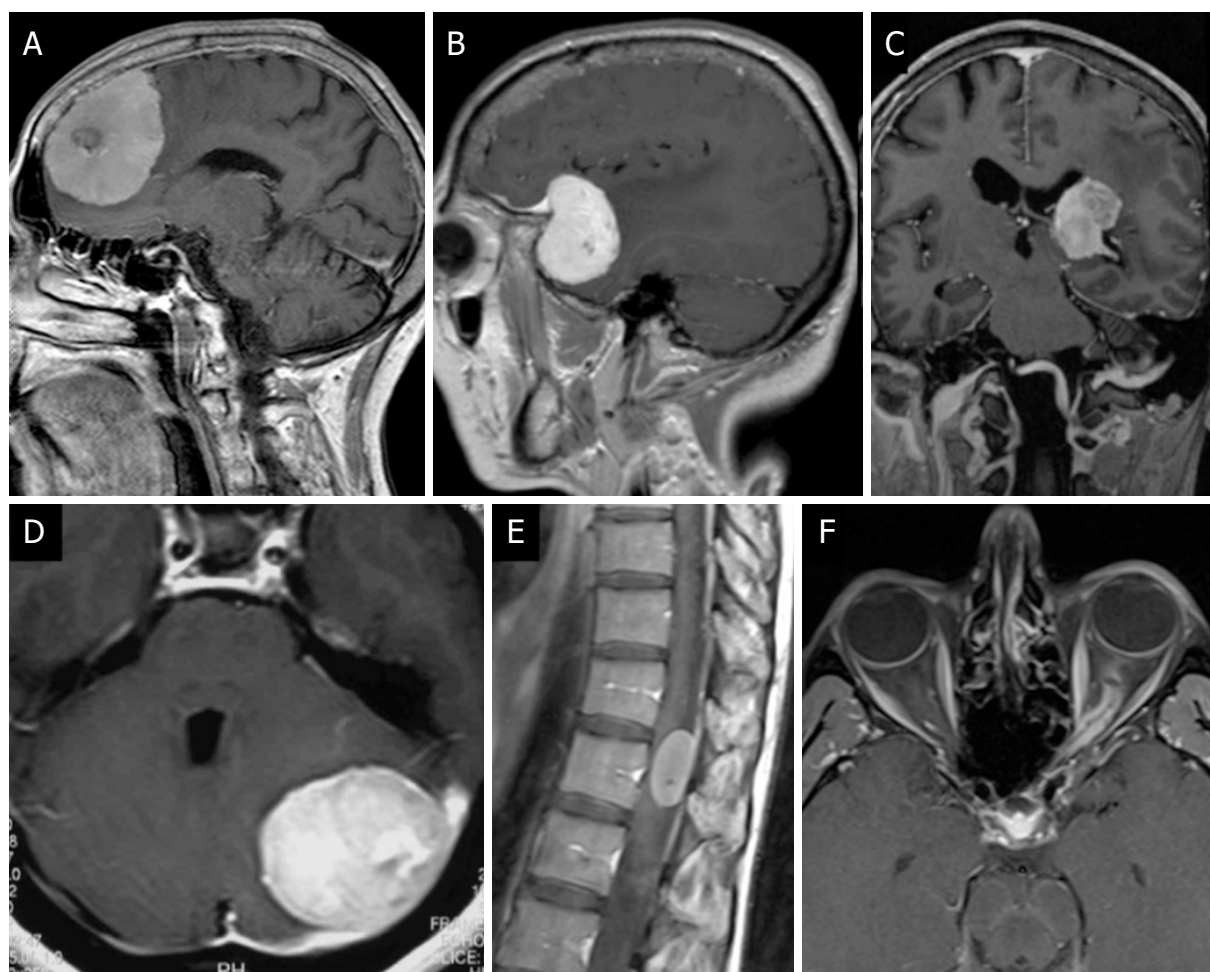


Figure 1. Post-contrast T1w images showing some of the possible different localizations of meningiomas along the neuroaxis: falx cerebri (A); sphenoid wing (B); intra-ventricular (C); tentorium (D); dorsal spine (E); and left optic nerve (F)

decades) and female patients (at least in part due to endogenous estrogen stimulation), their incidence is higher in the case of ionizing radiation exposure and in familial predisposing syndromes such as Type 2 neurofibromatosis; in these latter cases, they are generally multiple, with more severe symptoms and common atypical locations (for example, intraventricular or at the skull base)^[1,4].

Meningiomas are usually benign and slow-growing extra-axial tumors with poor tendency to metastatic dissemination and local aggressiveness. Due to their relatively benign biologic behavior, meningiomas are frequently discovered incidentally during CNS imaging and for smaller ones a watchful waiting strategy can be envisaged. However, despite largely being considered a purely benign disease, meningiomas can also cause high morbidity and mortality due to focal neurological deficits, potentially difficult surgical resectability, and local aggressiveness; these features can cause extremely severe repercussions in terms of symptoms severity, functional limitations, and quality of life^[1]. Due to this variability, the most recent 2016 World Health Organization (WHO) classification of CNS tumors proposed a revision of meningiomas classification, including the presence of necrosis, brain invasion, high cellularity, and elevated mitotic index with increase in small cells composition as diagnostic criteria for atypical meningiomas (Grade II-III tumors)^[5]. While atypical high-grade meningiomas are associated to a worst prognosis, higher survival rates are reported for low-grade meningiomas; however, also in these cases neurological deficits and long-term disability are a common complication.

With this knowledge, neurosurgical gross-total resection still represents the gold standard for patients' treatment, with radiotherapy used as adjuvant treatment in the case of non-radically removed lesions (whereas external-beam radiation was not demonstrated to be associated to better results compared to surgery followed by adjuvant radiation)^[6,7]. Surgical planning largely relies on MRI and CT scans examination, as the type of surgery performed can vary depending on tumor size and location. Different surgical techniques have been used for meningiomas. The most common approach is represented by craniotomy, in which brain exposure ensures tumor visualization on the brain surface, minimizing the risk of damaging adjacent structures. Another possible alternative is represented by neuroendoscopy-assisted microscopic resection techniques. Neuroendoscopic surgery is largely used for meningiomas within the ventricular chambers, whereas for ventral skull base meningiomas a possible option is represented by endoscopic endonasal surgery; however, while for olfactory groove or tuberculum sellae this latter approach has been widely validated, its use remains controversial in other skull base regions (such as cavernous sinus, petro-clival, or cranio-facial regions). Moreover, since meningiomas obtain vascular supply from extracranial and intracranial circulation, preoperative embolization can be used in selected cases as adjuvant therapy to reduce intraoperative bleeding and make surgery more effective; specific imaging techniques (such as perfusion and angiography) can provide information on meningioma's perfusion status, amenability to embolization based on blood supply, and eventual anatomical references that could help in the delivery of embolic materials. After partial resection, the disease-free survival rates range between about 60% at five years and 10% at 15 years, with ever-increasing tendency to recurrence over time. Nevertheless, also in the case of complete surgical removal, the overall rate of meningioma recurrence remains not negligible, as it is estimated to range 15%-25% at 20 years^[8,9].

With this background, it can be easily understood why neuroimaging plays a crucial role not only in meningioma first diagnosis, but also in therapeutic planning and long-term surveillance (for early detection of both recurrence in treated patients and disease progression in untreated ones). Here, we review the conventional findings in meningioma imaging, discuss the role of advanced diagnostic techniques, and offer an overview on possible future neuroimaging applications for lesions' characterization.

CONVENTIONAL IMAGING

Intracranial meningiomas

Intracranial meningiomas typically show characteristic neuroimaging features well detected on both CT and MRI studies, which allow the correct diagnosis with high diagnostic accuracy. MRI is the gold standard technique for meningiomas detection and evaluation because it provides soft tissue characterization, high contrast definition and possibility of multiplanar reconstructions^[10]. Meningiomas appear as extra-axial dural-based masses, with the exception of en plaque meningioma, exhibiting sheet-like appearance due to its extensive dural extrinsecation^[11]. On conventional MRI, they usually are hypo- to isointense on T1-weighted sequences, with variable signal on T2-weighted sequences due to the presence of necrotic cystic or calcific areas; most of them are avidly and homogeneously enhancing after paramagnetic agents administration [Figure 2]^[12,13]. T2w images also allow for crescent-shaped cerebral-spinal fluid (CSF) cleft between tumor and brain parenchyma identification, while post-contrast sequences allow for the detection of the characteristic dural tail, due to adjacent dural reactive changes^[14]. Edema in surrounding brain tissue is evident in about half of cases, generally due to the presence of atypical features related to a more aggressive biological behavior rather than to overall dimension^[15]; on diffusion-weighted images (DWI), brain edema is typically vasogenic, due to different mechanisms such as venous obstruction, pial vessel paralysis, and vessel barrier alteration^[16-19]. DWI has also been used to depict higher-grade meningiomas with increased cellularity, which show reduced values on corresponding apparent diffusion coefficient (ADC) maps^[20-22]; however, it should be noted that the correlation between DWI and tumor grade remains controversial, as no univocal statistical correlation between ADC values and tumoral behavior has been established yet^[23]. Other imaging characteristic that have been proposed as indicative of a more aggressive

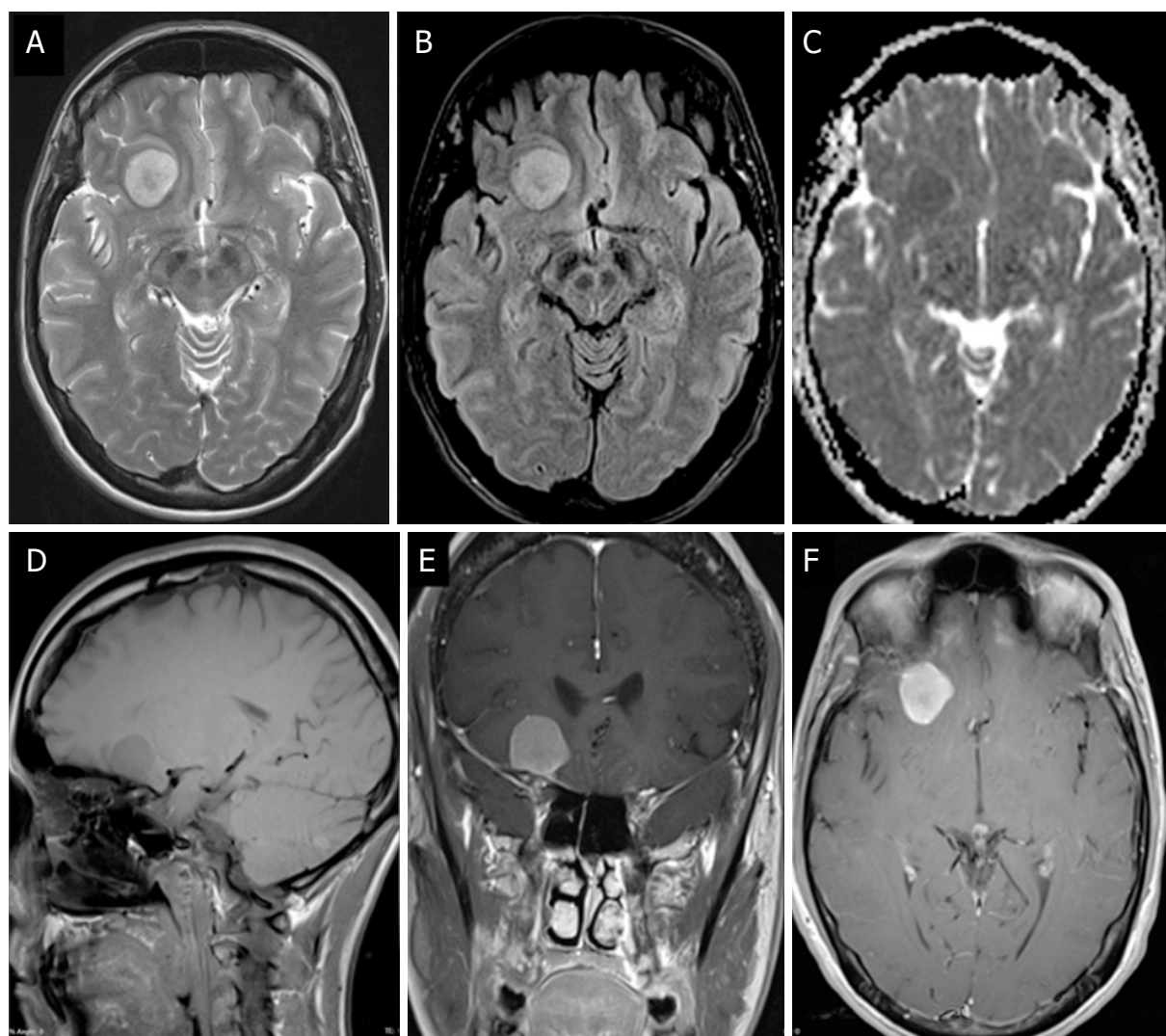


Figure 2. Right frontal low-grade meningioma on conventional MRI: hyperintense on T2w (A) and FLAIR (B) images, with no peripheral edema and a subtle crescent-shaped CSF cleft between tumor and adjacent brain tissue; no significant DWI restriction with moderate-to-high value on ADC map compared to brain parenchyma (C); and iso-hypointense relative to cerebral grey matter on T1w (D), with homogeneous and intense post-contrast enhancement (E, F). CSF: cerebral-spinal fluid; DWI: diffusion-weighted images; ADC: apparent diffusion coefficient

behavior include irregular margins, undefined tumor–brain interface, intra-tumoral necrosis and cysts, and absence of calcifications on susceptibility-weighted sequences [Figure 3]^[24]. Along with MRI, CT remains the gold standard for the depiction of tumor-induced osseous changes such as remodeling with focal hyperostosis and bone thickening or bone invasion with associated osteoblastic reaction (more rarely osteolysis) in malignant cases^[25]. Finally, meningiomas are highly vascularized tumors, being the blood supply provided by meningeal or vertebral-basilar branches; intra-tumoral dysplastic vessels can be better characterized in unenhanced and contrast-enhanced MR angiography. Conversely, MR venogram is usually performed to study venous sinuses invasion thrombosis or occlusion; while unenhanced phase-contrast MR venogram (and also black-blood MR imaging) has been demonstrated as a reliable method in assessing sinus invasion, it should always be considered that higher sensitivity in detecting collateral anastomoses and draining veins around the lesion is obtained with contrast-enhanced MR venography. This information is important both for surgical planning and for sinus preservation in the case of radiotherapy/radiosurgery^[17-19].

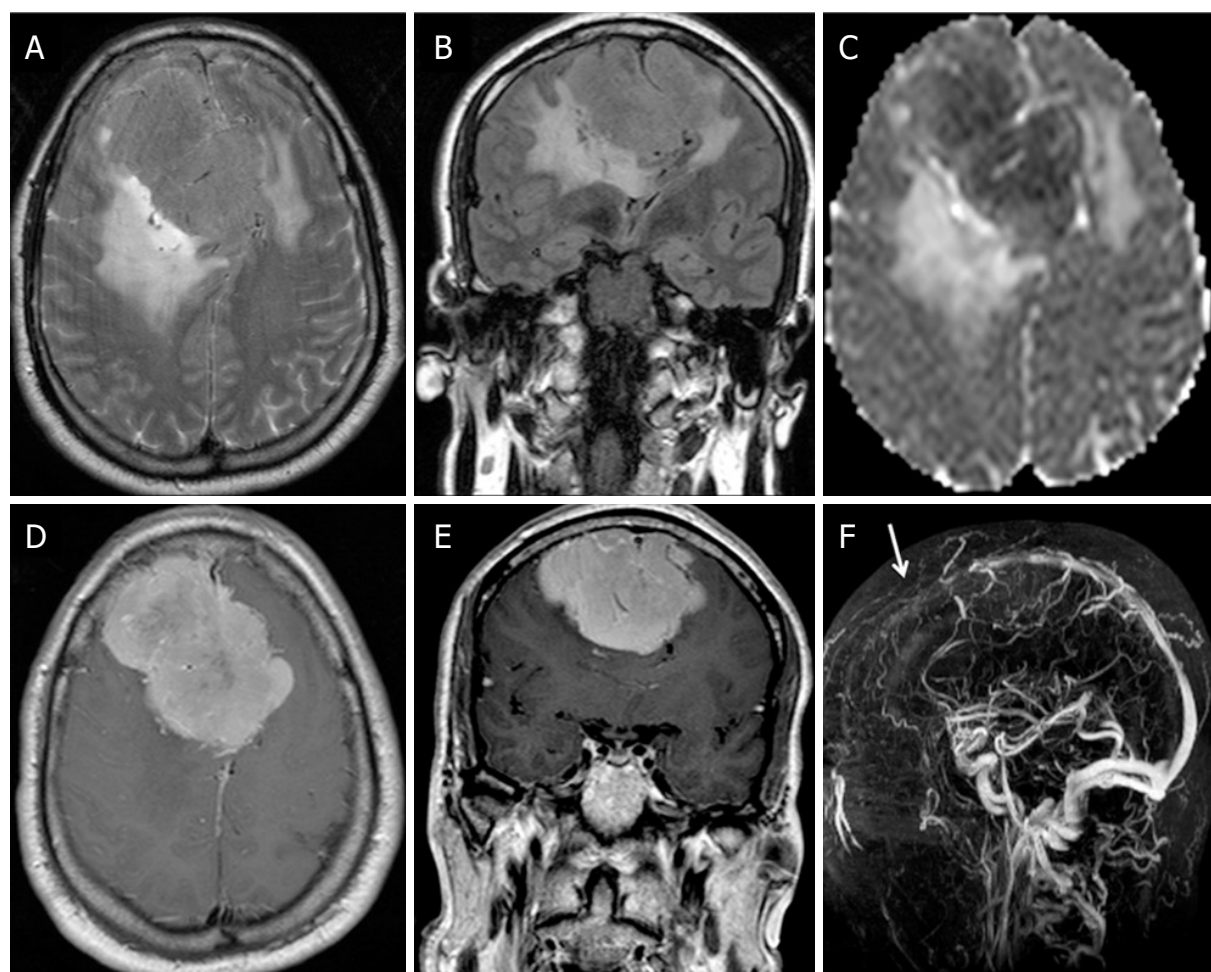


Figure 3. Falx cerebri high-grade meningioma on conventional MRI: inhomogeneous on T2w due to calcifications and necrosis (A), with large peripheral edema halo and no clear distinction from normal brain tissue on FLAIR (B); lower values compared to normal brain parenchyma on ADC maps (C); intense and inhomogeneous post-contrast enhancement after i.v. gadolinium administration (D, E); and invasion of the anterior segment of sagittal sinus on 3D PCA venogram (F). ADC: apparent diffusion coefficient

Spinal meningiomas

Spinal meningiomas are extra-spinal intra-dural well-defined masses, with only few cases arising from epidural compartment with both extra- and intra-dural extension (the latter are usually more aggressive, with higher risk of recurrence)^[26,27]. MRI of the spine represents the modality of choice for both diagnosis and follow-up; characteristics are similar to intra-cranial meningiomas, with a slightly lower signal on T2w compared to the spinal cord^[28]. Calcifications are less common than in intra-cranial compartment and more often reported in epidural lesions. Yeo *et al.*^[29] classified spinal meningiomas in four main subgroups, based on neuroimaging features: intradural homogeneous neoplasm avidly enhancing, with or without dural tail (Type A); round tumors with hypointense area on T2w images (Type B); en plaque meningiomas with a collar-like growth along spinal cord (Type C); and other meningiomas with atypical features (Type D)^[29,30]. Epidural meningioma, a rare entity classified as Type D, is often misdiagnosed due to its peculiar location; typical enlargement of neuroforamina determined by epidural growth pattern can be used as differential diagnostic feature^[31].

ADVANCED TECHNIQUES: POSSIBLE APPLICATIONS

Conventional MRI generally responds adequately to diagnostic purposes, however differential diagnosis between extra-axial dural-based masses (or between different meningioma subtypes) can be very

challenging. Tissue characterization, identification of important features for surgical planning, and prognostic biomarkers individuation can be enhanced by the use of advanced imaging techniques.

Spectroscopy

Spectroscopy is an MRI technique used to assess metabolite concentration in a region of interest. Therefore, it can be used for differential diagnosis both to differentiate between intra- and extra-axial masses and to exclude the hypothesis of dural metastases in the case of extra-axial dural-based mass in oncologic patients. Meningiomas show elevated choline and decreased N-acetylaspartate as well as decreased creatinine, a metabolic profile common to other neoplastic processes and therefore quite unspecific; conversely, increased alanine has demonstrated to be specific for meningioma but can be difficult to identify^[32,33]. An elevated metabolite peak at 3.8 parts per million has been described in meningiomas, allowing to differentiate them from high-grade gliomas and intracranial metastasis. MR spectroscopy has been demonstrated to not be able to differentiate atypical meningiomas from typical ones^[34,35]. Lactate peak is considered suggestive of aggressiveness, but it can also be found in benign meningiomas. Nevertheless, lactate and macromolecular peaks have demonstrated significant differences in meningothelial, fibrous, and oncocytic subtypes, showing the potential to characterize various lesion components^[36].

Perfusion imaging

MR perfusion is a technique used to assess blood flow in tissues and includes the dynamic susceptibility contrast (DSC) technique and the dynamic contrast enhancement (DCE) technique, both requiring the administration of intravenous gadolinium, and arterial spin labeling. Meningiomas are highly vascular lesions, deriving their blood supply from meningeal arteries and consequently demonstrating very high perfusion. The complete lack of the blood-brain barrier determines increased contrast leakage and permeability, represented by a typical time-intensity curve: rapid drop during the first pass of contrast and slow return to a level lower than brain parenchyma^[37]. MR perfusion can be useful in differential diagnosis, in particular to differentiate meningiomas from dural-based metastases and from high-grade gliomas invading the dura mater. Indeed, MR perfusion may differentiate between meningioma and dural metastases from various origins (breast, colon, and prostate) but not from hypervascular metastases, such as those from melanoma, renal carcinoma, or Merkel cell carcinoma (increased cerebral blood volume)^[38]. The assessment of the time-intensity curve can distinguish a primary glial neoplastic process from intracranial metastases/meningiomas: in the former, the curve shows more than 50% return to baseline, while, in the latter, the curve shows less than 50% return to baseline due to breakdown in blood-brain barrier and dural-based blood supply. Meningioma vascularity appears to be significantly related to cerebral blood flow (CBF) values^[39-41] and lately a significant correlation between CBV and expression of vascular endothelial growth factor has also been demonstrated, suggesting the possibility to use perfusion MR to predict refractoriness to conventional treatment and possible responsiveness to anti-angiogenic therapies. Correlation between relative CBV (rCBV) and Ki67 proliferative index has also been demonstrated in meningiomas but several studies have shown contrasting results about a possible correlation between tumoral perfusion parameters and meningioma grade, probably because of increased vascular permeability of meningiomas, due to lack of blood-brain barrier^[22,42,43]. On the contrary, peritumoral rCBV has shown a potential diagnostic role: although peritumoral rCBV usually shows decreased values in meningiomas, possibly due to peritumoral vasogenic edema^[44], its values are higher in the case of anaplastic meningiomas (WHO Grade III) compared with the other types^[45]. Similarly, decreased peritumoral CBF can be measured with CT perfusion, potentially representing ischemic tissue salvageable after meningioma resection^[46]. Arterial spine labeling has the advantage of assessing perfusion without the confounding permeability influence, potentially allowing to differentiate WHO Grade I from WHO Grades II and III intracranial meningiomas^[47]. Vascular permeability represents another measurable parameter, assessed directly via DCE technique and contributing to meningioma grading: atypical meningiomas have shown higher values of Ktrans compared with benign meningiomas^[48]. MR perfusion can be helpful also in distinguishing some

meningioma subtypes. In particular, angiomatous meningioma has demonstrated higher tumor rCBV compared with meningothelial, fibrous, or anaplastic subtypes^[45].

Diffusion tensor imaging

Given the possibility to assess magnitude and directionality of water diffusion, diffusion tensor imaging (DTI) has been applied to differentiate meningioma grades. Although in most studies high-grade meningiomas have demonstrated low ADC values when compared with low-grade ones, controversial results have been obtained especially for the other DTI parameters^[49-51]. DTI has shown promising potential in terms of preoperative consistency prediction. Besides some contrasting findings, most studies have shown higher fractional anisotropy (FA) values in hard meningiomas compared to soft ones^[52-54]. Signal intensity on FA and mean diffusivity maps have also been found to be predictive of meningioma consistency^[52,53,55]. Tractography, derived from DTI data, may give additional information for treatment planning of skull base meningiomas, but it is usually not necessary: resolving the course of cranial nerves with CSF sensitive sequences is technically easier and less sensitive to artifacts^[12].

MR elastography

MR elastography (MRe) is a promising emerging technique that may have the potential to define tumor consistency and its relationship with adjacent structures. It provides a measurement of tissue stiffness, determined by the assessment of shear wave movement through that given tissue. Recent studies have demonstrated a significant correlation between the MRe measurements and intraoperative qualitative assessment of tumor consistency^[33]. Furthermore, differing stiffness on both sides of a tissue boundary allow defining the measurement of freedom of the adjacent tissue planes, thus evaluating the marginal invasiveness^[56].

Molecular imaging

The most used molecular imaging technique in oncological field is 2-^[18F]-fluoro-2-deoxy-D-glucose (18F-FDG)-PET, which uses a glucose analog to identify metabolically active cells, but it does not have a primary role in intracranial tumors diagnosis due to high physiological FDG uptake in cerebral cortex and FDG accumulation in inflammatory processes. The ability of FDG-PET to differentiate meningioma grades has shown contrasting results. Although some studies have demonstrated its ability to differentiate benign meningioma from atypical/malignant ones and to distinguish recurrent/growing meningiomas from static ones, there is a lack of correlation between FDG uptake and WHO grading, MIB-1 labeling index, and tumor doubling time^[12]. On the other hand, a high meningioma-to-background contrast can be obtained using radiolabeled somatostatin receptors II (SSTR II) ligands due to the increased expression of SSTR II in meningiomas compared to the very low expression in bone and brain tissue^[57,58]. PET with gallium-68-labeled SSTR-ligands, such as 68Ga-DOTATOC (DOTA-(Tyr3)-octreotide) and 68Ga DOTATATE (DOTA-DPhe1-Tyr3-octreotate), has demonstrated a higher sensitivity in detecting meningiomas when compared to contrast enhanced MRI^[59]. SSTR-PET is also useful for differential diagnosis, for example when studying optic sheath meningioma^[60]. This technique also allows a detailed meningioma extent delineation, necessary for treatment planning but challenging in the case of complex localization (skull base, orbit, falx cerebri, sagittal, and cavernous sinuses), trans-osseous growth, or in pre-treated meningiomas, when MR contrast results are limited^[12,61]. Integration of SSTR-PET imaging increases the precision of resection and target radiation. Furthermore, SSTR-PET can differentiate viable tumor and scar tissue using a semi-quantitative data analysis, since semi-quantitative uptake values (SUV) correlate significantly with SSTR II expression assessed by immunostaining. Patient treatment stratification can take advantage of SSTR-PET since SUV measurements have also demonstrated a correlation with tumor growth rate in WHO Grades I and II meningiomas (not in Grade III). Furthermore, SSTR-PET has been demonstrated to be more specific for detecting residual meningioma and may be considered in the case of equivocal MRI findings^[62-64]. Recently, the RANO-PET taskforce has proposed an evidence-based recommendation for the use of

molecular imaging in meningiomas, even if the utility of SSTR II imaging needs more validation to be confirmed^[65].

FUTURE DIRECTIONS

Radiomics is an emerging field of research that extracts many features from medical images. There are two categories of features, which can be extracted from the region of interest after the lesion segmentation, semantic and agnostic ones. In detail, semantic features are commonly used in the radiology lexicon to describe a lesion (e.g., shape, location, *etc.*), but in the radiomics field they are quantified through computer assistance. On the other hand, diagnostic features describe lesion heterogeneity using quantitative descriptors. They include first-, second-, or higher-order statistics. First-order statistical outputs consist of the grey level histogram analysis of the lesion's voxels. Second-order statistics are those obtained from texture analysis. They describe relationships between voxels considering their contrast values. Finally, higher-order statistics are obtained imposing filters to extract definite image patterns, such as fractal analyses, wavelets, or Laplacian transforms of Gaussian bandpass filters^[66]. Radiomics can be coupled with artificial intelligence, which employs algorithms to allow computers to learn directly from the data and make predictions on unseen datasets, because of its better capability of managing this volume of data compared to traditional statistics^[67]. In the study of meningiomas, radiomics and artificial intelligence have shown promise in preoperative evaluation, recurrence and outcome prediction, and radiation treatment planning. Preoperative prediction of the meningioma grade is important because it influences the treatment strategy. Park *et al.*^[68] obtained an accuracy of 89.7% for the prediction of meningioma grades using MR conventional and diffusion tensor imaging with a radiomics and machine learning approach; furthermore, various texture parameters differed significantly between fibroblastic and non-fibroblastic benign meningiomas. Volumetric assessment of meningiomas is also highly relevant for therapy planning and monitoring. Using a multiparametric deep-learning model on routine MRI data, Laukamp *et al.*^[69] investigated its performance in automated detection and segmentation of meningiomas in comparison to manual segmentations, obtaining a strong correlation despite diverse scanner data. Moreover, prognostic models based on clinical, radiologic, and radiomic feature have been investigated to preoperatively identify meningiomas at risk for poor outcomes. In this setting, preoperative radiologic and radiomic features such as apparent diffusion coefficient and sphericity have proved effective in predicting local failure and overall survival in these patients^[70]. MR radiomics has also been implemented to predict early progression or recurrence, which characterize a subset of skull base meningiomas, achieving good results (accuracy 90%)^[71]. Finally, radiomics has proved useful in the definition of radiotherapy target volume, which represents a critical step in treatment planning, in order to improve the texture-based differentiation of tumor from edema and to differentiate vasogenic from tumor cell infiltration edema^[72].

CONCLUSION

Although generally easily identified on the basis of some pictorial neuroimaging features, meningiomas can raise some concerns in terms of tissue characterization and treatment selection. In particular, surgery largely relies on MRI and CT scans examination, as the type of therapeutic approach can vary depending on tumor size and location. Modern imaging tools are helpful in identifying more aggressive histological behavior, defining vessel and brain involvement, and evaluating the need for adjuvant therapies; at the same time, emerging post-processing techniques can enhance tumor biology tracking and response to therapy prediction. All these imaging-derived data coupled together may allow for optimal therapeutic planning and tailored longitudinal follow-up, based on both patient and tumor fingerprinting.

DECLARATIONS

Authors' contributions

Made substantial contributions according to ICMJE criteria: Elefante A, Russo C, Di Stasi M, Vola E, Ugga L, Tortora F, De Divitiis O

Conception and design: Elefante A

Writing: Russo C, Di Stasi M, Vola E, Ugga L
Supervision: Tortora F, De Divitiis O

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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

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Case Report

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Reticular patterned episcleral venous plexus and 360-degree episcleral venous fluid wave after hemi-gonioscopy assisted transluminal trabeculotomy

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Abstract

We describe a method for eliciting an episcleral venous fluid wave (EVFW) in eyes presenting with reticular patterned episcleral venous plexus, after a hemi-gonioscopy assisted transluminal trabeculotomy (hemi-GATT). To reduce the risk of post-operative hyphema and reduce intraoperative tissue manipulation, a hemi-GATT (targeting 180-degrees of Schlemm's canal) was performed. Post-hemi-GATT, the ability to inject balanced salt solution and obtain an EVFW in both the treated (inferior) and untreated (superior) sectors of the eye supports the surgical success of the technique, and demonstrates an enhanced fluid outflow and subsequent vessel blanching. The pre-operative intraocular pressure of 20/21 mmHg in a single subject decreased to 18-, 12- and 15-mmHg after one day, one month and 3 months post-op, respectively, and the subject was rendered medication-free. This method of performing a hemi-GATT to effectively obtain an EVFW provides evidence for novel treatment algorithms in patients with a reticular episcleral venous plexus where identification of major outflow vessels is less apparent.

Keywords: Gonioscopy assisted transluminal trabeculotomy, micro-invasive glaucoma surgeries, glaucoma surgery, episcleral venous fluid wave



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INTRODUCTION

Glaucoma stands as the leading cause of irreversible blindness worldwide and approximately 3% of the population between 40-80 years old have a primary open angle glaucoma^[1]. While a trabeculectomy is considered as the gold standard treatment for glaucoma management, the use of micro-invasive glaucoma surgeries (MIGS) for the treatment of mild to moderate glaucoma are growing due to their high safety profile, rapid recovery time, and minimally invasive nature^[2,3]. Canal-based MIGS procedures attempt to bypass the trabecular meshwork, a major site of resistance to aqueous humor drainage, and enhance the conventional outflow^[4]. While the true efficacy of MIGS procedures is still to be elucidated, surgeons are discovering that device design and surgical expertise are not the sole determinants of treatment success. The placement of these devices in terms of optimal orientation to best enhance aqueous outflow is of paramount importance, giving rise to the term “targeted MIGS”. Implantation of iStents (Glaukos Corporation, Laguna Hills, CA, USA) is one such canal-based procedure. However, current literature supports implantation of one to three iStents in areas of dense trabecular pigmentation, adjacent to major aqueous and episcleral veins that are identified via external examination and/or in areas of focal blood reflux in the Schlemm canal as seen with gonioscopy, in an attempt to target the major collector channel ostia in anterior segments^[4]. The rationale is to target these large capacity veins to effectively enhance aqueous drainage. We describe a reticular patterned episcleral venous plexus that comprises of a network of numerous small-caliber, finer vessels, rather than a few, large-caliber vessels.

Gonioscopy assisted transluminal trabeculotomy (GATT) is a novel, ab interno MIGS approach to a 360-degree trabeculotomy that is conjunctival-sparing while also resulting in successful reductions in intraocular pressure (IOP) and decreased need for glaucoma medications^[5]. A hemi-GATT unroofs 180-degrees of the Schlemm's canal to reduce the risk of postoperative hyphema and reduces intraoperative tissue manipulation. Both a 360 degree-GATT and hemi-GATT aim to improve aqueous outflow through Schlemm's canal and adjacent collector channels^[5]. Unlike in filtration surgery where bleb morphology correlates with surgical success, to date there is no concrete evidence, whether pre-operative, intraoperative or post-operative, of a similar association between bleb morphology and canal-based MIGS surgery^[3]. However, growing evidence supports the correlation between the presence of an episcleral venous fluid wave (EVFW) and post-operative reductions in IOP as well as the need for fewer glaucoma medications and/or additional surgeries^[3]. An EVFW is an intraoperative technique performed at the conclusion of a surgery wherein diffuse vessel blanching is achieved by injecting balanced salt solution (BSS) that flows into the conjunctival and episcleral venous systems, demonstrating possible patency of the conventional aqueous outflow system^[3,6]. For an EVFW to be present, fluid must be able to travel from collector channel openings, through the deep and mid scleral plexuses to the episcleral plexus terminating in the conjunctival veins, thereby demonstrating an enhanced aqueous outflow^[3].

Due to the broad 180- to 360-degree area of treatment with hemi-GATT and GATT procedures respectively, theoretically, one could propose that these procedures could be effective even in eyes demonstrating a reticular patterned episcleral venous plexus as one could target large areas of Schlemm's canal rather than individual veins to enhance aqueous drainage. We propose that hemi-GATT is an effective technique to enhance aqueous outflow in eyes that have a reticular patterned episcleral venous plexus, with EVFW serving as an indicator of probable surgical success.

CASE REPORT

Description of the surgical technique

Using standard sterile eye preparation, the surgical eye was draped and held open with a wire lid speculum. The inferior sector of the eye (inferior 180-degrees) was selected as the hemi-GATT target. The hemi-GATT was performed using the ripcord technique, modified from that described by Grover *et al.*^[5] [Figure 1, Video 1].

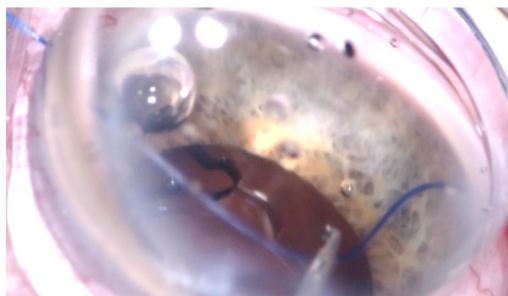


Figure 1. Hemi-gonioscopy assisted transluminal trabeculotomy performed with ripcord technique in the inferior sector.



Figure 2. External ocular examination post-hemi-gonioscopy assisted transluminal trabeculotomy showed a reticular episcleral venous pattern in the superior and inferior sectors. Note that the reticular pattern is more pronounced in the superior sector (left of image).



Figure 3. Reducing the intraocular pressure results in engorgement of the episcleral venous plexus superiorly and inferiorly.

The procedure for EVFW generation, as described below, was based on that described by Fellman *et al.*^[3,6].

Post-hemi-GATT, the gonioscopy lens was removed for external examination of the episcleral vasculature both adjacent to the treated site (inferior sector) and in the untreated superior sector. The reticular pattern of the episcleral venous plexus was noted in both sectors [Figure 2]. In the mid-anterior chamber, an irrigation/aspiration probe was used to remove the residual viscoelastic substance that was left behind by the hemi-GATT at an irrigation pressure of 65 mmHg. When closely observing the adjacent episcleral veins, the IOP in the anterior chamber was reduced by halting fluid irrigation until episcleral veins filled with blood and focal blood reflux was seen into the anterior chamber adjacent to the surgical site (inferior sector). At this point, there was maximal prominence of the reticular episcleral venous pattern in both the superior and inferior sectors [Figure 3]. Toward the end of the surgery, at the time of BSS injection, the episcleral vessels were closely observed for vessel blanching from the BSS washout. Hyperinfusion with BSS post-hemi-GATT created an EVFW with progressive vessel blanching in both the treated inferior



Figure 4. Hyperinfusion of the anterior chamber with balanced salt solution causes an episcleral venous fluid wave and blanching of both the superior and inferior sectors.



Figure 5. Reducing the intraocular pressure to near-physiologic conditions results in a prominent reticular episcleral venous pattern in the superior, untreated sector (left of image). Note that there is still some residual blanching in the inferior, treated sector (right of image).

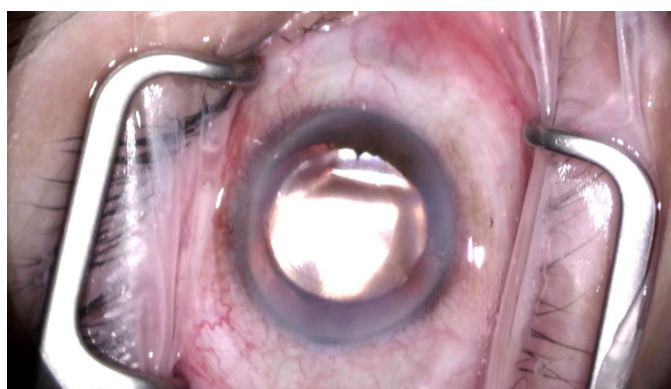


Figure 6. Hyperinflation of the anterior chamber with balanced salt solution to supraphysiologic conditions results in a 360-degree limbal blanching during the episcleral venous fluid wave.

and untreated superior sectors [Figure 4]. Reducing IOP to near-physiologic conditions resulted in a prominent reticular episcleral venous pattern in the superior, untreated sector; residual blanching remained in the treated, inferior sector [Figure 5]. Repeated hyperinflation of the anterior chamber with BSS to supraphysiologic conditions results in 360-degree limbal blanching during EVFW [Figure 6], and when IOP is lowered, there was a 360-degree engorgement of the episcleral venous plexus [Figure 7].

Results/Case study

This procedure was performed on the right eye of a 58-year-old female with pigmentary glaucoma in both eyes. The pre-operative IOP was 20/21 mmHg as measured with Goldmann tonometry, and the subject



Figure 7. When the intraocular pressure is lowered, there is a 360-degree engorgement of the episcleral venous plexus.

took topical pressure-lowering medication of travaprost, once daily. Prior to the surgery, external ocular examination revealed a reticular episcleral venous plexus with a diffuse interconnected meshwork of veins and venules. The post-operative IOP decreased to 18 mmHg, 12 mmHg and 15 mmHg, on day one, one month and 3 months post-op, respectively. At 3 months post-op, the patient was not taking any pressure-lowering medications. Blanching of the episcleral venous plexus due to the EVFW was observed post-operatively in both the superior and inferior sectors.

DISCUSSION

Glaucoma is the leading cause of irreversible blindness worldwide with an increasing prevalence in the aging population^[1]. When a surgical treatment is desired to halt or slow down the disease progression, canal-based MIGS surgeries are typically favored^[6]. The focus of these procedures is to enhance the physiological aqueous outflow, generally as an alternative to those requiring formation of an artificial external bleb^[6]. Canal-based MIGS procedures attempt to bypass the area of greatest resistance to aqueous outflow, the trabecular meshwork, and thus enhance aqueous drainage^[1,7]. MIGS devices like the iStent (Glaukos Corporation, Laguna Hills, CA, USA) are heparin-coated titanium stents, designed to enhance aqueous outflow through the conventional outflow pathway^[2]. However, to be effective, the stent must be placed to target large capacity veins that support drainage directly from Schlemm's canal rather than from smaller venules that drain distal plexuses^[2,8]. Recent studies suggest that implantation of two iStents, instead of three, results in similar reductions in IOP, inferring therefore that proper device placement rather than the device number most likely dictates surgical success^[1]. However, a problem arises when patients present with a reticular patterned episcleral venous plexus because identifying the ideal target for iStent implantation becomes increasingly difficult.

Reticular episcleral venous patterning is seen as an interconnected meshwork of veins and venules where clear large capacity outflow veins cannot be easily identified. This is in contrast to detecting discrete, large-caliber episcleral veins. To the best of our knowledge, other *in vivo* patterns of the episcleral venous plexus have not yet been defined. In eyes with a reticular patterned episcleral venous plexus, it would be possible to implant numerous iStents, approximately 1-2 clock hours apart, spanning the venous plexus. If the surgeon uses a direct view gonioscope that requires tilting of the patient's head and microscope, implanting more than 3 iStents can become surgically challenging because the easiest access from a temporal approach is the nasal 180 degrees of Schlemm's canal. Furthermore, the cost of the surgery increases with each additional implanted device. Potentially, using iStent inject devices combined with a direct-view gonio mirror that does not require tilting the microscope allows one to treat the full 360-degrees of the trabecular meshwork. As demonstrated in this case study [Figures 6 and 7], we achieved a full 360-degree EVFW with a 180-degree unroofing of Schlemm's canal with a hemi-GATT.

As shown, eyes presenting with a reticular patterned episcleral venous plexus are good candidates for procedures like the hemi-GATT that target a larger sector of Schlemm's canal. Not only was there a reduction in IOP, but there was also an elimination of medication burden associated with glaucoma. Furthermore, since the subject presented with a diffuse reticular pattern, one might have been tempted to perform a GATT to target the entire drainage system circumference. However, previous preliminary results comparing the success rates for the GATT and hemi-GATT show no significant difference (success rate of 74% for GATT and 70% hemi-GATT)^[9]. Herein, the hemi-GATT was shown to enhance drainage in both the superior and inferior sectors while preserving the superior 180-degrees of Schlemm's canal to enable future angular surgery, if needed.

When determining the approach to performing a hemi-GATT, a surgeon must choose the sector to target. Due to the ease of surgical access, the nasal quadrant is most commonly favored as the location for Schlemm's canal surgeries. However, surgical ease is not the sole reason for this target. The nasal quadrant is also the location of the highest density of collector channels^[2]. With 25-35 collector channels per eye, one desires to target as many of these as possible when performing a hemi-GATT to maximize conventional aqueous flow^[3]. To exit the eye via the conventional pathway, aqueous fluid must pass through the collector channels for subsequent drainage into the deep venous scleral plexus, the mid scleral plexus and the episcleral plexus to finally reach the conjunctival veins^[3]. While no clinically established marker has yet been proven to conclusively predict the likelihood of success with canal-based MIGS procedures, growing evidence supports the presence of an EVFW as a marker of surgical success^[3,6]. Research has shown that the ability to elicit a pronounced EVFW with diffuse blanching of the visible vessels correlates with the need for fewer medications and lower postoperative IOP^[3]. It is theorized that eyes with a positive EVFW must have patent collector channels and a downstream outflow system for the infused BSS to blanch the episcleral vessels^[3]. As demonstrated here, the inferior 180-degrees incorporating the infra-nasal quadrant serves as an optimal location for hemi-GATT to best enhance aqueous outflow. Despite leaving the superior 180-degrees of the eye untreated, diffuse episcleral venous blanching in this area was observed with BSS infusion. In some patients, treatment of a section of Schlemm's canal may be sufficient to achieve the desired surgical outcome.

In conclusion, a hemi-GATT targeting the inferior 180-degrees of Schlemm's canal is a MIGS procedure that is applicable to eyes demonstrating a reticular pattern episcleral venous plexus. The ability to elicit a pronounced EVFW post-hemi-GATT that was seen in both the superior untreated sector and the inferior treated sector, indicates patency of the collector channels and enhanced aqueous outflow via the conventional outflow pathway. Further work may help determine the ideal glaucoma surgical procedure based on a patient's particular episcleral venous pattern.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study, and performed data analysis and interpretation: Wiens J, Gooi M, Schlenker M, Gooi TL, Wentzell D, Gooi P

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Patrick Gooi is a consultant for Alcon, Allergan, Bausch and Lomb, Glaukos, and Santen. He has a patent on a glaucoma device.

Matt Schlenker is a consultant for Abbvie, Alcon, Bausch Health, J&J, Thea-Labtecian, Santen, and Zeiss.

Ethical approval and consent to participate

Research was performed in accordance with the Declaration of Helsinki and approved by the Health Research Ethics Board of Alberta.

Consent for publication

Not applicable.

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Case Report

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Clostridium difficile infection secondary to ileostomy closure

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Abstract

Protective ileostomy may be a risk factor for the development of *Clostridium difficile* (CD) infection (CDI). In the postoperative period signs of CDI may be particularly difficult to differentiate from intra-abdominal sepsis. Presented here are 2 cases that developed CDI after ileostomy reversal. Two patients who underwent low anterior resections after neoadjuvant chemoradiation with protective ileostomy developed fever, leukocytosis and elevated serum C-reactive protein (CRP) levels. The first patient also had negative CD stool toxins and his signs were so severe that he underwent a negative diagnostic laparoscopy and re-creation of ileostomy. The second patient who presented in a similar fashion was more fortunate in that her CD stool toxin was positive and she was treated successfully with oral vancomycin. CDI after ileostomy reversal after low anterior resection can be difficult to diagnose. In the first patient, the situation was so misleading that diagnostic laparoscopy was required. Outcome was eventually favorable in both cases. CDI must be high on the list of differential diagnoses for febrile patients with a leukocytosis and elevated CRP level even in the setting of negative CD stool toxins. Prophylactic intravenous metronidazole and/or vancomycin enemas should be considered prior to colorectal surgery when a protective ileostomy is likely.

Keywords: Clostridium difficile, stoma, cancer, rectal, laparoscopy, surgery, pseudomembranous colitis



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INTRODUCTION

Proximal fecal diversion through a loop ileostomy is commonly used to protect colorectal anastomosis. Patients undergoing total mesorectal excision (TME) for rectal cancer are at higher risk of developing an anastomotic leak^[1]. Diverting stomas were found to decrease both the clinical anastomotic leak rate and the risk of re-operation in patients undergoing low anterior resection or TME^[2]. The temporary stoma is usually closed 8 to 12 weeks after surgery, or even earlier^[3] when there are no clinical or radiological signs of leak. *Clostridium difficile* infection (CDI) is a major cause of hospital-acquired infection that continues to increase in incidence and severity among hospitalized patients^[4,5]. Symptoms range from mild diarrhea to fulminant colitis causing severe sepsis, toxic megacolon, and even death. The major risk factors for acquiring CDI are previous antibiotic exposure, severe underlying disease, older age, and immune suppression^[4,5]. In this paper, we report on an unusual presentation of CDI in 2 patients who had an elective reversal of ileostomy after TME for rectal cancer. The initial presentation of CDI mimicked more common causes of postoperative intra-abdominal sepsis.

CASE REPORT

Case # 1

A 47-year-old woman, with an unremarkable past medical history was diagnosed with low rectal adenocarcinoma. She underwent trans-anal TME^[6] with diverting loop ileostomy 10 weeks after the completion of a neoadjuvant treatments, including 45-Gr external beam radiotherapy and oral 5-fluorouracil. Her postoperative course was uneventful. Final pathology diagnosed a pT1pN0 adenocarcinoma with an R0 resection. Fourteen days after resection, the patient underwent ileostomy closure after digital exam, endoscopy, and a computerized tomography (CT) scan showed no evidence for an anastomotic leak. She received one dose of intravenous antibiotics (cefuroxime 1 g IV) at the induction of anesthesia. The immediate postoperative outcome was uneventful.

However, 3 weeks postoperatively, the patient started having lower abdominal pain and severe diarrhea with over 10 bowel movements per day. Physical examination revealed a fever at 38.5 °C, a heart rate of 92 BPM, and blood pressure at 110/70 mmHg. Abdominal examination was within normal limits and did not reveal any signs of superficial surgical site infections. Gynecological evaluation was negative for sepsis. Serum blood tests revealed a leukocytosis with white blood count of 13,500/mm³ and an elevated C-reactive protein (CRP) at 132 mg/L. Stool testing for *Clostridium difficile* toxin was negative. As symptoms worsened with persistent fever, a pelvic magnetic resonance imaging (MRI) scan was performed and revealed evidence suggestive for a leak of the colo-anal anastomosis [Figure 1].

A diagnostic laparoscopy was performed. More than 2 liters of clear liquid was found in the peritoneal cavity that ultimately tested negative for bacteria, fungus, creatinine, bilirubin, or amylase. There were no signs of intestinal perforation or ureteral injury; however, the colon was hypervascularized, thickened, and dilated. A loop ileostomy was again performed.

Postoperatively, stool cultures became positive for *Clostridium difficile* (CD). Intravenous metronidazole was administered for 48 h then orally for 10 more days. Clinical improvement occurred rapidly.

Case # 2

A 64-year-old man, with a past medical history of hypertension, type 2 diabetes mellitus, and coronary artery disease, was diagnosed with low rectal adenocarcinoma. He underwent trans-anal TME with diverting loop ileostomy, 11 weeks after neoadjuvant treatment, including 45-Gr external beam radiotherapy and oral 5-fluorouracil. His initial postoperative course was uneventful. Pathology report showed a pT3pN0 adenocarcinoma with an R0 resection. Eight weeks after surgery, the patient had

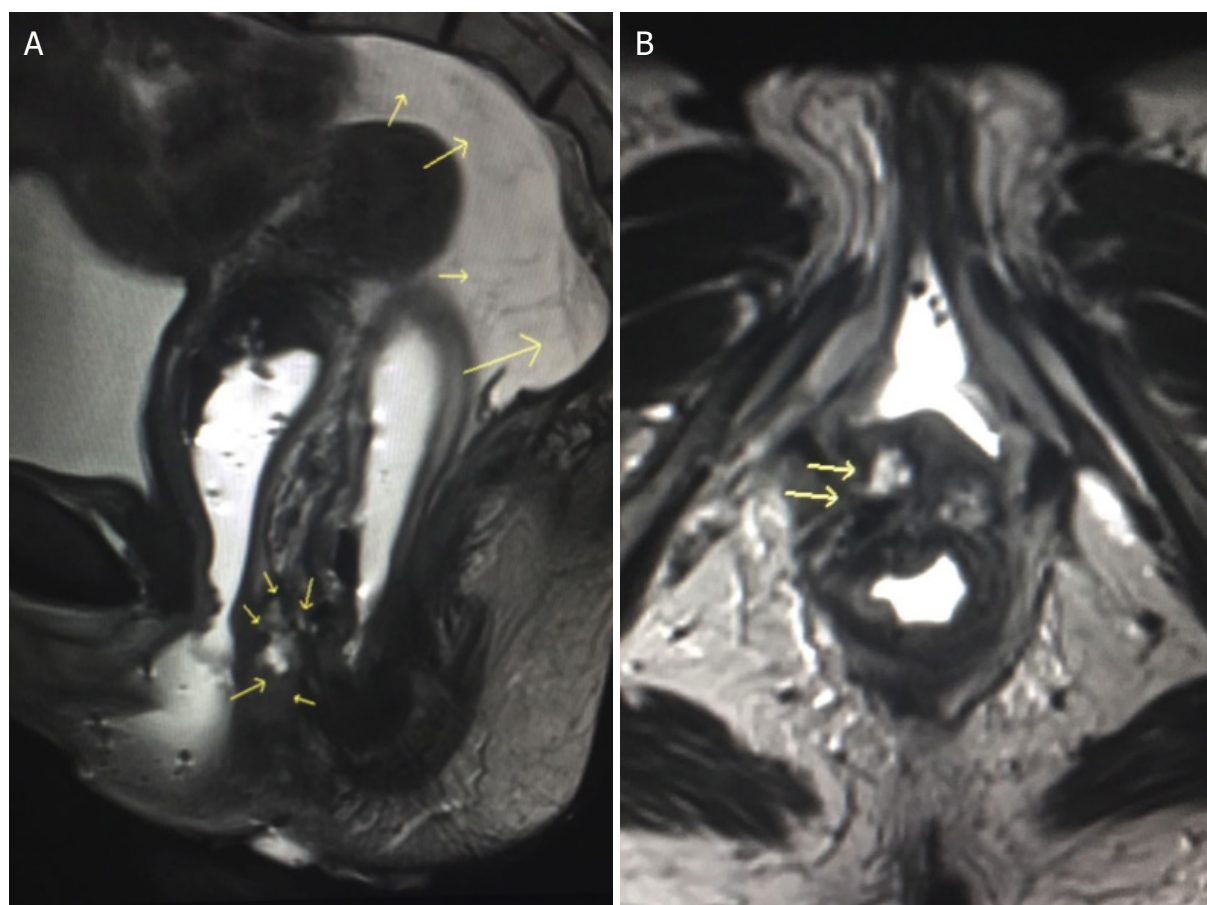


Figure 1. Pelvic magnetic resonance imaging (MRI) scan in a 47-year old woman with pain and febrile diarrhea 2 weeks after total mesorectal excision (TME) with colo-anal anastomosis: (A) small arrows in a circle at the bottom of the image show fluid next to the colo-anal anastomosis evoking leak. Large arrow on the right of the image shows massive intra-peritoneal fluid. Note the concern for colonic wall thickening (horizontal arrow); (B) small arrows show what was considered as extravasation of contrast in the vicinity of the colo-anal anastomosis.

ileostomy closure after a normal pelvic CT scan with contrast. He received one dose of prophylactic antibiotics (cefuroxime 1 g IV) at the induction of anesthesia. The immediate postoperative outcome was uneventful. Ten days postoperatively, the patient started having diffuse abdominal pain and watery diarrhea with 6 to 7 bowel movements per day. Physical examination revealed fever at 39 °C, tachycardia at 112 BPM, and hypertension at 170/100 mmHg. Abdominal examination, including digital rectal examination, was normal. Blood chemistries were consistent with acute renal failure (blood urea nitrogen at 61 mg/dL; creatinine at 2.9 mg/dL), leukocytosis with white blood count at 23,000/mm³, and increased CRP at 252 mg/L. Stool testing for toxin-producing CD was positive. Treatment was with 2 g of oral vancomycin for 10 days. The patient's renal function fully recovered without the need for dialysis. Neither patient received adjuvant chemotherapy.

DISCUSSION

Symptoms of CD colitis such as pain, diarrhea, and increased CRP may be indistinguishable from other causes of intra-abdominal sepsis (i.e., anastomotic leak, pelvic abscess, or iatrogenic bowel injury). This could cause delay in the diagnosis of CDI, which could be fatal^[7]. In the literature, we could only find a few papers that reported CDI after closure of ileostomy^[7-11]. In some reported cases, as in our first case, the presentation was confusing, and the diagnosis was delayed. In another case, the disease was even much more severe (fulminant colitis), and the patient deteriorated quickly and died following an emergency total colectomy^[7].

Three studies looked more closely into the incidence of CD after ileostomy closure^[12-14]. Hussain *et al.*^[12] prospectively evaluated 20 patients undergoing ileostomy reversal. Two stool samples were collected before and after the procedure and tested for CD and toxins A and B. None of the patients had positive tests preoperatively. Two of the 20 patients had asymptomatic postoperative CD colonization (10%), while one patient developed clinical CDI with positive toxins (5%). Randall *et al.*^[13] retrospectively analyzed patients who had ileostomy closure and subsequent CDI. Six (4.2%) of the 143 patients who had ileostomy reversal developed CDI. In a retrospective large population-based analysis (2004-2008) in the US, Wilson *et al.*^[14] found the incidence of CDI after ileostomy closure to be 1.6%.

There is no clear explanation yet for the high rate of CDI after ileostomy closure. Theoretically, CD could colonize the small bowel, with many studies reporting symptomatic enteritis. Animal studies have shown that excluded colons undergo mucosal and muscular atrophy with derangement in the intestinal immune system. The exclusion of the colon could change the unique microbial ecosystem in the large bowel and favor the growth of CD. When the stoma is closed, the spores could get reactivated and enter a growth phase leading to clinical infection.

We suppose that the prophylactic antibiotics administered at the induction of anesthesia at the index operation may have triggered the CDI in our 2 cases. Previous studies have reported that the risk of subsequent CDI was 5.9-fold higher among patients colonized with toxigenic CD upon hospital admission as compared to non-colonized patients^[15]. In our protocol, patients are tested for CD colonization before all colorectal resections. Both patients in our study were negative preoperatively. Besides antibiotics as well-known risk factors for CDI^[16], other incriminating factors include previous hospitalization within 3 months^[15], chemotherapy within the previous 8 weeks^[17], or even gastric acid suppression with proton pump inhibitors (PPIs)^[18].

Rubio-Perez *et al.*^[19] reported a significant association between CDI and delayed ileostomy reversal (of greater than 6 months), with the reported dysfunctional time ranging from 9 to 15 months. Our two patients underwent ileostomy closure less than 2 months after the first surgery. Neither patient received PPIs, and both had stopped their oral chemotherapy more than 3 months earlier. A meta-analysis published in 2017 found that the incidence of CDI after ileostomy reversal was 1.8%. It also suggested that probiotics should be considered, PPIs avoided, and rectal swabs considered in high-risk patients, and that when possible ileostomy closure should be scheduled within 6 months^[20].

Despite its low incidence, the clinical presentation of CDI may be indistinguishable from the usual postoperative state. Therefore, diagnosis could be challenging. Since fulminant cases are known to occur, clinicians must consider this condition in the differential diagnosis. Prompt evaluation is warranted in patients undergoing ileostomy reversal who present with severe diarrhea and abdominal pain. Clinicians should be aware of the risk factors for CDI. Systematic preoperative testing of colonization with CD should be encouraged. We also recommend reducing the use of unwarranted antibiotics and PPIs.

Although neither of these patients required adjuvant chemotherapy, and the best timing of ileostomy closure during or after adjuvant treatments has not been well established, one should consider early ileostomy reversal where appropriate, even if it does not seem to completely prevent CDI. Considering the nature of the topic and question, the highest level evidence that can potentially be achieved in this context is from case-control studies (level 3) and meta-analysis of observational studies (level 2-3). Notably, a meta-analysis did not see any difference in outcomes whether ileostomies were reversed during or after adjuvant treatments^[21]. Prophylactic use of vancomycin enemas in the excluded colons prior to ileostomy closure is an option to be further evaluated^[22]. Additionally, metronidazole should potentially be added to the preoperative regimen when a protective ileostomy is envisioned.

DECLARATIONS

Authors' contributions

Data analysis and interpretation, drafting of manuscript, and editing: Chouillard E, Gumbs AA
 Performed data acquisition and data analysis: Chouillard MA, Kary NE
 Provided administrative support and editing: De Simone B

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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Technical Note

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Mastering TAPP inguinal hernia repair-tips and tricks

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Abstract

Laparoscopic minimally invasive surgery is increasing, and in the last decade some modifications of the technique have been introduced, especially concerning mesh type, fixation, and peritoneal closure, which are herein individually discussed. Currently, a standard unique technique is still missing, and modifications of the technique might be useful in challenging cases, such as the use of fibrine glue to both fix the mesh and close the peritoneum. The aim of this technical note essay is to discuss and update some tips and tricks as well as recent modifications of the trans-abdominal preperitoneal (TAPP) repair of groin hernia.

Keywords: Inguinal hernia, trans-abdominal preperitoneal, laparoscopic surgery

INTRODUCTION

Over the last decade, laparoscopic inguinal hernia repair has gained worldwide popularity due to several advantages, in particular the faster recovery and reduced postoperative pain compared to the open approach with superior cost-effectivity^[1-3]. Since the description of the laparoscopic trans abdominal preperitoneal (TAPP) repair, the technique has undergone several modifications, such as the mesh type and fixation and the method to approximate the peritoneum, with the aim of making the procedure easier and improving results^[3-5]. These modifications have also been included to face some challenging cases where the standard procedure cannot be applied. Currently, it is important that training surgeons master these modifications and the technique, including some tips and tricks, which is the aim of this technical note essay.



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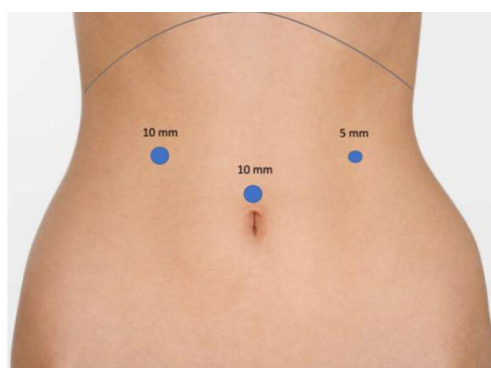


Figure 1. Trocars placement.

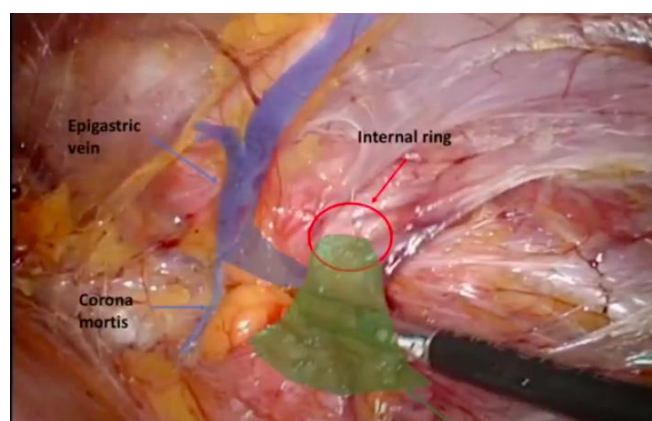


Figure 2. Surgical field.

Surgical technique at our center

A single dose of first-generation cephalosporin is given at the induction of anesthesia. The operation is performed under general anesthesia with the pneumoperitoneum established through a Veress needle in the left subcostal space, as has been previously described^[3]. Three trocars are placed, as shown in [Figure 1](#). The peritoneum is opened approximately at the level of the lateral trocar and extended medially in the direction of the superior margin of the internal inguinal ring, up to the residue of the umbilical artery. When the Cooper ligament is exposed, the hernia sac is isolated and reduced, freeing the spermatic cord [[Figure 2](#)]. The entire video can be viewed at: <https://youtu.be/6EILTdWhoI>.

Postoperative pain: the main issue of laparoscopic inguinal hernia repair

Persistent postoperative pain after placement of staples to secure the mesh, along with the discovery of the “triangle of doom” and “triangle of pain”, have led to the recommendation of using only a few staples or replacing them with glue^[2]. This eliminates the risk of lateral cutaneous femoral nerve entrapment, which is the main cause of chronic pain. The same suggestions are extended to the closure of the peritoneum, replacing staples as much as possible with suture or glue^[2]. These modifications might increase the immediate costs. However, apart from the clinical advantages, these may entail some cost savings in the long term that only a real cost-effectiveness analysis can detect.

The type of mesh used, its fixation, and the peritoneal closure for the TAPP technique are still some of the most important topics under discussion, as several modifications of the procedure have been proposed since its first description^[2-5].

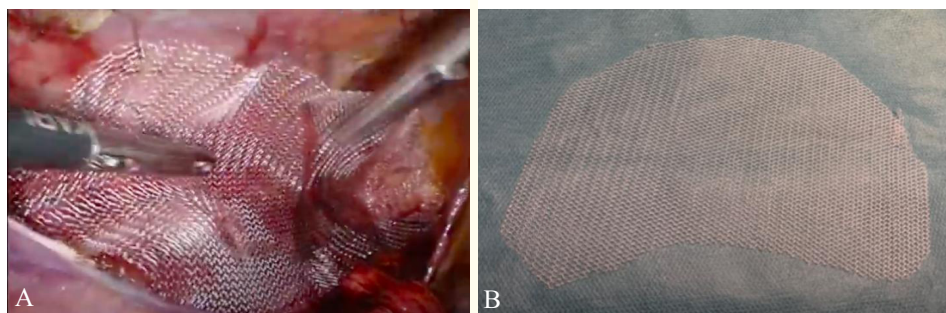


Figure 3. Self-cut polypropylene mesh placement (A, B).

Mesh type

Several meshes are available for minimally invasive inguinal hernia repair^[4,5]. The surgeon must consider several factors when choosing a mesh for hernia repair including clinical outcomes, cost, and ease of use.

There are specific laparoscopic meshes with a rigid border that facilitates their placement in the preperitoneal space. However, the issue with these meshes is their size, as sometimes they do not fit within our dissection area. It happens that the surgeon is forced to enlarge the preperitoneal space to place the mesh. Another issue is its higher cost, which, for certain health systems, cannot be afforded.

Self-fixating meshes are also available and very useful, as no further fixations tools are required. However, its placement is not easy, which represents the main reason for its low application among surgeons.

Sometimes, it happens that we work in a hospital without these types of meshes. Therefore, it is important to deal with the classical mesh, used for the open approach, and cut them to be adapted for the laparoscopic technique.

In this latter case, our suggestion is to use a polypropylene mesh and to cut it into a shape of almost 10-15 cm to be introduced into the abdominal cavity in the preperitoneal space, as shown in [Figure 3](#).

Fixation of the mesh

Several randomized studies have shown that using staples for mesh fixation might cause high early postoperative pain and chronic pain^[6,7]. Therefore, it is suggested to minimize their use as much as possible by applying only one staple to the Cooper ligament or by using self-fixating meshes^[2,6,7].

Currently, there is not enough evidence to avoid fixing the mesh in the preperitoneal space, as increasing numbers of recurrences have been described^[3].

Some authors have reported their experience avoiding the use of staples and securing the mesh with glue only, such as fibrine glue or cyanoacrylate^[7,8].

Mesh fixation with fibrine glue was proven to be safe and effective in the prospective randomized trial of Lovisetto *et al.*^[8], published more than a decade ago, and it was associated with a lower incidence of postoperative neuralgia compared with staples.

In light of these results, after some time, we modified our TAPP technique where staples were used for both mesh and peritoneal closure to avoid staples altogether and replace them with fibrine glue to fix the mesh.



Figure 4. Fibrine glue specific tool placement.

The mesh is secured with approximately 2 mL of fibrine glues (Tisseel, Baxter Healthcare), applied as shown in Figure 4, at almost 1 cm distance from the mesh, using a specific laparoscopic tool.

This tip is very useful especially in those cases where a non-specific laparoscopic mesh is used, as their structure does not fit in the preperitoneal space as with the specific mesh type.

Peritoneal closure

The original TAPP technique includes staples to both fix the mesh and close the peritoneum. This might be the fastest and easiest method, but at the price of a higher risk of nerve injury and bleeding, since staples may damage nerves and vessels^[9]. To decrease chronic pain, some absorbable staples have been introduced. However, the potential decrease of bleeding cannot be avoided.

Currently, the most frequently used modification is that of the running suture to close the peritoneum. However, suturing the peritoneum is not as easy as it seems; it remains a challenging maneuver, requiring specific surgical skills to avoid tears or ruptures that may expose the mesh to the intestine, with secondary obstruction or fistulation. With the attempt to further decrease the difficulty of this procedure, barbed sutures have been introduced. However, even with this suture, it still requires some skills, and the peritoneum closure time step, even with barbed suture, may require longer time compared with the overall surgical step. With running suture, peritoneal ruptures still occur, especially in cases when the hernia sac reduction maneuver has been particularly challenging (such as with large sliding hernias, where the flap peritoneum is very thin and too weak to be closed with a suture or in cases with a large amount of fat in the peritoneum, adding difficulty to its closure for increased tension). In addition, it is important to state that running suture of the peritoneum does not avoid the risk of nerve entrapment or bleeding, as the suture of the superior flap of the peritoneum frequently includes part of the abdominal wall. Even if not well described in the literature, epigastric vessels have been frequently injured during the closing of the peritoneum. When this occurs, it is challenging to face it. For this reason, there is a need for some modifications of the technique that may not be the standard but are useful in those difficult cases.

For these cases, our specific tip is to use, when it is required, fibrine glue.

The most frequently studied glue product is N-2-butyl cyanoacrylate. It shows a great capacity for both mesh and peritoneal closure that is achieved after only a few seconds^[10]. However, being a non-biological glue, one of the main criticisms is that, when this product is in contact with the intestine, strong adhesions may develop. Nevertheless, the study of Wilson *et al.*^[10], which recently investigated their experience with cyanoacrylate mesh and peritoneal closure, reported excellent results with no long-term complications. However, considerable precautions are required when using this product in order to avoid dropping any material into the intestine.

An alternative to cyanoacrylate is the biological human fibrine, which has the double function of both glue and hemostatic. Different from cyanoacrylate, there is more evidence in the literature that fibrine glue may prevent peritoneal adhesions, and it may represent the optimal and safest method to close the peritoneum^[11]. We believe that the key advantage of the modified technique, where we completely replace the running suture with fibrine glue to approximate the peritoneum, is particularly useful for those cases where the peritoneum is at a higher risk of tear or rupture during closure.

According to our experience, in our previous published study, we were able to show a decreased operative time of the procedure while also maintaining acceptable postoperative outcomes and quality of life^[3]. To date, this is the unique study showing long-term results using fibrine glue to both fix the mesh and close the peritoneum.

Furthermore, according to our experience, we found the peritoneal closure with fibrine glue a simple to learn and master maneuver that does not require specific skills.

CONCLUSION

Tips and tricks

Avoid use of stapler to fix the mesh and close the peritoneum.

The knowledge of some alternatives of the technique are paramount in challenging inguinal hernia repairs, for example: Peritoneal closure can be performed using glue when its closure is challenging. When a specific mesh is not available, it is paramount to know how to prepare it.

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

Not applicable.

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Original Article

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Laparoscopic Roux-en-Y gastric bypass for excess weight and diabetes: a multicenter retrospective cohort study in China

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Abstract

Aim: The aims of this study were to better understand the outcomes of Roux-en-Y gastric bypass (RYGB) surgery in patients across multiple hospitals in China along with patients with type 2 diabetes mellitus (T2DM) and to explore the potential preoperative predictors of diabetes outcomes after RYGB.

Methods: This was a retrospective cohort study in Chinese patients who underwent laparoscopic RYGB at five Chinese hospitals from April 2009 to December 2014 and returned for follow-up approximately one-year post-



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surgery. The STROCSS guideline checklist was applied.

Results: In total, 130 patients underwent RYGB: 85 males and 45 females; age, 43.4 ± 11.3 years; and preoperative body mass index (BMI), 33.1 ± 9.0 kg/m². Of those, 103 (79.2%) had T2DM duration of 6.6 ± 4.7 years and pre-RYGB HbA1c of $8.1 \pm 1.9\%$. Among the patients with T2DM, glycemic control (HbA1c < 7.0%) increased from 28.7% before surgery to 79.3% at 12 months post-procedure, with a concurrent reduction in the use of anti-hyperglycemic agents, including a reduction in insulin requirement from 55.4% to 27.0%. The percentage of excess weight loss was $-42.8 \pm 44.2\%$. Among 71 patients with T2DM and data about remission status, 14 (19.7%) achieved T2DM remission at 12 months post-surgery. Age and duration of T2DM were lower in the remission group, while baseline BMI and weight were higher compared with the non-remission group.

Conclusion: RYGB may be effective for weight loss and T2DM control in Chinese patients, and outcomes are consistent with the literature in Western populations. Younger patients with T2DM and with a higher BMI pre-surgery and shorter duration of T2DM were more likely to achieve T2DM remission.

Keywords: Type 2 diabetes, obesity, roux-en-Y gastric bypass, glycemic control, remission

INTRODUCTION

World Health Organization (WHO) estimates that 422 million adults globally were living with type 2 diabetes mellitus (T2DM) in 2014 and that the prevalence of T2DM has doubled since 1980^[1]. China has almost 115 million patients with T2DM, with an adult diabetes prevalence of 9.8% that is rapidly increasing, presenting in individuals with higher insulin resistance but with lower body mass index (BMI) and approximately 10 years younger than their Western counterparts^[2-4]. A review of the literature about bariatric surgery in China showed a significant increase in the number of procedures performed in China between 2001 and 2015 (a total of 7779 procedures in this period, from 47 surgeries during 2001-2005 to 795 during 2006-2010 and 6937 during 2011-2015); in addition, the proportion of procedures performed to treat obesity-related comorbidities (defined as metabolic surgery) increased from 0% of the total number of procedures performed in 2001 to 70% by 2015^[5].

While the growing obesity pandemic is considered a major factor in the growth of T2DM prevalence^[6], central adiposity, not BMI *per se*, is considered a primary factor in the rise of T2DM in China^[7] and other regions of Asia^[8]. BMI distributions in the adult populations differ between the United States and China. Approximately 31% of adults in China^[9] are classified as overweight (BMI ≥ 24 to < 28.0 kg/m²) and 12% as obese (BMI ≥ 28 kg/m²) compared to 40% obese (BMI ≥ 30.0 kg/m²) and 8% severely obese (BMI ≥ 40.0 kg/m²) in the United States in 2016^[10]. Therefore, the WHO has defined obesity in terms of abdominal obesity, a waist-hip ratio above 0.90 for males and 0.85 for females, or a BMI > 30.0 kg/m²^[6,11] and has recommended health action (such as bariatric surgery) in Asians with T2DM at a BMI 2.5 kg/m² lower than in other ethnicities (i.e., BMI 27.5 kg/m² vs. 30.0 kg/m²). Globally, bariatric metabolic surgeries such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy have emerged as the most effective interventions for sustained weight and diabetes control in patients who are obese^[11]. Given the burden of disease in China, metabolic surgery is being undertaken in some patients at even lower BMI^[12,13]. Studies showed that laparoscopic RYGB could be beneficial in patients with BMI < 28 kg/m², or even < 27.5 kg/m²^[12,13].

Although the surgical techniques have been described extensively, evidence of laparoscopic RYGB in Chinese patients who are overweight or obese, with or without T2DM, is still limited. This multicenter study aimed to examine the health outcomes after RYGB surgery and determine the potential preoperative predictors of diabetes remission after RYGB surgery.

METHODS

Study design

This was a retrospective cohort study in Chinese patients who underwent an RYGB procedure between April 2009 and December 2014 at five Chinese academic urban hospitals and returned for follow-up approximately one-year post-surgery. This study was approved by each site's ethics committee, including a waiver for informed consent due to the retrospective nature of this study. The study was registered at ChiCTR.org.cn (#ChiCTR-OOC-15006387). The study was reported in accordance with the STROCSS guideline checklist^[14].

The inclusion criteria were: (1) underwent an RYGB procedure; (2) aged 20-60 years; and (3) had outcome data recorded [at least one of glycated hemoglobin (HbA1c), fasting plasma glucose, or fasting insulin levels] in their medical charts at approximately 12 months after surgery.

Study interventions

All participating hospitals assessed each patient who underwent RYGB through a multidisciplinary and integrated health unit, including a bariatric surgeon, endocrinologist, psychiatrist, cardiologist, and dietician. Weight, BMI, T2DM duration, anthropometric measures, systolic and diastolic blood pressures, glycemic control (HbA1c, fasting blood glucose, and insulin), lipid profile, and other laboratory and clinical evaluations recorded in the patient's medical record were analyzed. Given the retrospective design, not all outcome measures were available for all patients, and those outcomes available were not always available at all study time points.

Outcomes

The primary outcome was the resolution of T2DM. The secondary outcomes were weight reduction, improvements in glycemic control, vital signs, blood lipids, liver function, and adverse events (AEs).

Statistical analysis

The study was not statistically powered, and data from all patients who had an RYGB procedure during the study period and met the eligibility criteria were analyzed. For the total study population, interest focused on changes in anthropometric characteristics, vital signs, glycemic parameters, serum lipids, and liver function tests. In addition, for subjects with T2DM, changes in concomitant T2DM medication were of interest as well as the remission of T2DM, which was defined as fasting glucose levels < 110 mg/dL and HbA1c < 6.0% without the use of anti-hyperglycemic agents (AHAs) at 12 months after surgery.

Summary statistics for the outcome parameters were calculated, as well as their change from baseline. For all analyses, baseline was defined as the last available measurement taken on or before the date of RYGB surgery. For the mean change from baseline, 95% confidence intervals were estimated, and the one-sample *t*-test or the Wilcoxon rank-sum test was applied. No multiplicity adjustments were made to *P*-values for testing the change from baseline. Given the retrospective design of the study and sparseness of data at all available time points post-surgery for some parameters, the last observation carried forward (LOCF) approach was used. For each parameter, the latest value observed in the first 12 months after surgery was identified and used to evaluate the change from baseline to Month 12. Change in BMI was summarized by baseline BMI subgroup based on the WHO cutoff points. A significance level of 0.05 was considered statistically significant, and all reported *p*-values are nominal *P*-values.

To explore which factors could be associated with T2DM remission or non-remission, univariable and multivariable analyses were performed. Summary statistics for baseline demographic and clinical characteristics as well as post-surgery weight and BMI change were generated for patients with and without

Table 1. Demographics and baseline characteristics

Characteristic	Overall (<i>n</i> = 130)		T2DM (<i>n</i> = 103)	
	<i>n</i>	Mean ± SD/ <i>n</i> (%)	<i>n</i>	Mean ± SD/ <i>n</i> (%)
Age (years)	130	43.4 ± 11.3	103	46.2 ± 10.1
Sex				
Female	130	45 (34.6)	103	33 (32.0)
Male	130	85 (65.4)	103	70 (68.0)
BMI (kg/m ²)	127	33.1 ± 9.0	101	31.2 ± 7.9
Weight (kg)	130	94.7 ± 29.6	103	87.9 ± 24.2
Waist circumference (cm)	102	108.0 ± 21.4	86	104.2 ± 18.7
Female	35	108.2 ± 18.4	27	105.5 ± 19.3
Male	67	107.9 ± 22.9	59	103.6 ± 18.6
Waist-to-hip ratio	76	0.96 ± 0.10	75	0.96 ± 0.10
Female	24	0.93 ± 0.14	24	0.93 ± 0.14
Male	52	0.97 ± 0.06	51	0.97 ± 0.06
Duration of T2DM (years)	NA	NA	102	6.6 ± 4.7

BMI: Body mass index; NA: not applicable; SD: standard deviation; T2DM: type 2 diabetes mellitus.

T2DM remission. Logistic regression analyses with T2DM remission as the dependent variable were also performed using backward selection to determine what variables were independently associated with T2DM remission when considering all predictors simultaneously. All statistical analyses were performed with SAS®, Cary, NC.

RESULTS

Patient characteristics

In total, 130 Han Chinese patients met the eligibility criteria, of whom 103 patients (79.2%) had a diagnosis of T2DM. Demographics and baseline characteristics are presented in [Table 1](#).

Surgical interventions and outcomes

RYGB procedures and postoperative care were performed per the standard of care at each hospital. The mean length of the biliopancreatic limb was 74.9 ± 37.0 cm, and the Roux limb was 97.5 ± 36.6 cm. All 130 procedures were successfully completed laparoscopically across a broad BMI range of 20.8–65.3 kg/m² (2.4% for BMI 18.5 to < 23.0 kg/m²; 29.9% for BMI 23.0 to < 27.5 kg/m²; 27.6% for BMI 27.5 to < 32.5 kg/m²; and 40.2% for BMI > 32.5 kg/m²). The mean operative time was 179 ± 59 min. The mean length of stay (surgery-to-discharge) was 8.8 ± 5.7 nights.

For the total population, weight pre-surgery and at 12 months was available for 90 patients and was reduced by 16.5 ± 12.8%. Meaningful reductions in BMI were also observed (−6.2 ± 5.6 kg/m²) at 12 months with LOCF. Excessive weight loss was not observed as the lowest postoperative BMI reported was 18.1 kg/m². Meaningful improvements were also observed in the total population through 12 months for glycemic control, vital signs, blood lipids, and liver function [[Table 2](#)]. Among 53 procedure-related AEs, 24 (45.3%) were recorded as Clavien-Dindo Grade 1, 20 (37.7%) were Grade 2, and 9 (17.0%) were Grade 3. The more serious events (all Grade 3, no Grade 4) included ileus (*n* = 2), anastomotic leak (*n* = 1), anastomotic stenosis (*n* = 1), gastric fistula (*n* = 1), gastric ulcer (*n* = 1), intestinal obstruction (*n* = 1), post-procedural edema (*n* = 1), and small intestinal obstruction (*n* = 1). Six patients (4.6%) reported nine AEs within 30 days after the procedure, including five patients (six AEs) with GI disorders. Five patients experienced AEs requiring reoperation, and these AEs included small bowel obstruction, anastomotic leakage, anastomotic stenosis, ileus, gastric fistula, and anastomotic edema. Every AE requiring reoperation was resolved.

PATIENTS WITH T2DM AND RISK ANALYSIS

Following RYGB surgery in patients with T2DM, statistically significant and clinically meaningful improvements in anthropometric characteristics and laboratory values were observed 12 months after

Table 2. Anthropometric characteristics, vital signs, and laboratory values for patients with T2DM using last observation in Year 1 carried forward

Variable	n	Baseline	Month 12	Δ , 0 to 12 mo	P
Weight					
Weight (kg)	87	87.7 \pm 23.9	72.7 \pm 20.4	-15.0 \pm 15.2	< 0.001
Change in weight (%)	87	NA	NA	-15.9 \pm 12.5	< 0.001
%EWL [†]	87	NA	NA	-42.8 \pm 44.2	< 0.001
BMI (kg/m ²)	78	30.9 \pm 7.9	24.9 \pm 5.8	-6.0 \pm 5.5	< 0.001
Blood pressure					
Systolic blood pressure (mmHg)	88	129.4 \pm 13.8	123.0 \pm 14.3	-6.4 \pm 15.9	< 0.001
Diastolic blood pressure (mmHg)	88	80.3 \pm 9.2	77.6 \pm 9.4	-2.7 \pm 11.6	0.034
Glycemic outcomes					
HbA1c (%)	87	8.0 \pm 1.9	6.1 \pm 1.5	-1.9 \pm 2.2	< 0.001
FBG (mg/dL)	100	165.8 \pm 64.9	116.6 \pm 37.6	-49.2 \pm 70.3	< 0.001
Fasting C-peptide (ng/mL)	85	2.5 \pm 1.5	1.5 \pm 0.7	-1.0 \pm 1.4	< 0.001
Fasting insulin (miu/L)	75	19.4 \pm 14.9	7.7 \pm 8.8	-11.7 \pm 15.0	< 0.001
Serum lipids					
HDL-C (mg/dL)	95	44.6 \pm 12.1	51.0 \pm 14.7	6.4 \pm 114.0	< 0.001
LDL-C (mg/dL)	95	107.1 \pm 35.7	84.2 \pm 23.7	-22.9 \pm 33.9	< 0.001
Triglycerides (mg/dL)	94	229.9 \pm 254.4	120.7 \pm 155.7	-109.2 \pm 254.1	< 0.001
TC (mg/dL)	95	188.0 \pm 54.9	153.3 \pm 32.7	-34.7 \pm 58.5	< 0.001
Liver function					
ALT (U/L)	96	37.9 \pm 25.0	27.4 \pm 15.9	-10.5 \pm 27.8	< 0.001
AST (U/L)	88	30.1 \pm 16.5	25.1 \pm 14.1	-5.0 \pm 21.6	0.032

Data are shown as mean \pm standard deviation. [†]%EWL is based on a target BMI of 19.0 kg/m². ALT: Alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; %EWL: percent excess weight loss; LDL-C: low-density lipoprotein cholesterol; NA: not applicable; TC: total cholesterol.

surgery [Table 2]. There were significant reductions in the glycemic outcomes (HbA1c, fasting blood glucose, fasting c-peptide, and fasting insulin) from baseline to Month 12. In addition, patients had improved blood pressure values (systolic and diastolic), lipid values (increased high-density lipoprotein cholesterol and decreased low-density lipoprotein cholesterol, triglycerides, and total cholesterol), and liver function values (decreased alanine aminotransferase and aspartate aminotransferase). Patients lost 15.9 \pm 12.5% of their weight, with higher weight loss observed in those with higher BMI at baseline [Tables 2 and 3]. Severely obese individuals (BMI \geq 32.5 kg/m²) lost 20.7 \pm 16.5% of their weight on average. Figure 1 demonstrates an overall trend towards reduced health risk based on BMI classification. The only patient with BMI < 23 kg/m² remained in this category at 12 months. Among the 21 patients with BMI 23-27.5 kg/m² before surgery, 10 (47.6%) remained in the same BMI category, while 11 (52.4%) were downgraded to < 23 kg/m². Among the 32 patients with BMI > 27.5 kg/m² before surgery, 9 (28.1%) remained in the same BMI category, 13 (40.6%) were downgraded to 23-27.5 kg/m², and 10 (31.3%) were downgraded to < 23 kg/m². Therefore, 63% of the patients with T2DM reduced their WHO BMI risk category by at least one category after RYGB.

As shown in Figure 2, the percentage of patients diagnosed with T2DM and achieving glycemic control (HbA1c < 6.0%) significantly increased from baseline (11.5%) to 12 months post-procedure (56.3%). An overall reduction in the use of AHAs occurred during the first year after surgery [Figure 3], including a decrease in the number of patients with insulin requirement, from 55.4% at baseline to 27.0% over 12 months. Patients with T2DM requiring no AHA increased from 16.2% at baseline to 33.8% at 12 months post-procedure. The percentage of patients taking antihypertensive medication decreased (baseline to Month 12) from 28.4% to 18.9%, and those taking dyslipidemia medication decreased from 8.1% to 4.1%.

There were 71 patients with data available for the assessment of T2DM remission and any potential predictive factor. Fifty-seven patients (80.3%) showed improvements and near-remission and 14 patients

Table 3. Anthropometric characteristics and laboratory values for patients with T2DM (stratified by BMI group) using last observation in Year 1 carried forward

Variable	Δ , 0 to 12 mo							
	BMI Group 0 ($< 23.0 \text{ kg/m}^2$)		BMI Group I ($23.0 \text{ to } < 27.5 \text{ kg/m}^2$)		BMI Group II ($27.5 \text{ to } < 32.5 \text{ kg/m}^2$)		BMI Group III ($\geq 32.5 \text{ kg/m}^2$)	
	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD	n	Mean \pm SD
Weight								
Weight (%)	1	-13.4	34	-11.8 \pm 10.2	28	-16.9 \pm 9.8	24	-20.7 \pm 16.5
BMI (kg/m^2 %)	1	-8.2	31	-12.7 \pm 9.4	28	-18.0 \pm 9.4	18	-27.1 \pm 14.4
Glycemic outcomes								
HbA1c ($\Delta\%$)	1	-1.7	34	-1.6 \pm 2.2	27	-1.9 \pm 2.3	24	-2.5 \pm 2.1
FBG (mg/dL)	3	-16.9 \pm 19.8	35	-51.6 \pm 70.0	31	-36.2 \pm 78.1	30	-66.8 \pm 61.1
Serum lipids								
HDL-C (mg/dL)	3	-8.8 \pm 4.8	32	6.6 \pm 15.2	31	6.5 \pm 15.5	28	7.1 \pm 10.5
LDL-C (mg/dL)	3	-25.6 \pm 14.4	32	-15.5 \pm 40.6	31	-21.6 \pm 31.4	28	-32.7 \pm 29.0
Triglycerides (mg/dL)	3	-31.0 \pm 12.9	32	-158.5 \pm 393.1	30	-53.5 \pm 152.9	28	-123.3 \pm 112.2
TC (mg/dL)	3	-36.3 \pm 28.2	32	-26.4 \pm 59.1	31	-37.7 \pm 76.9	28	-41.5 \pm 33.7

BMI: Body mass index; FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation; TC: total cholesterol.

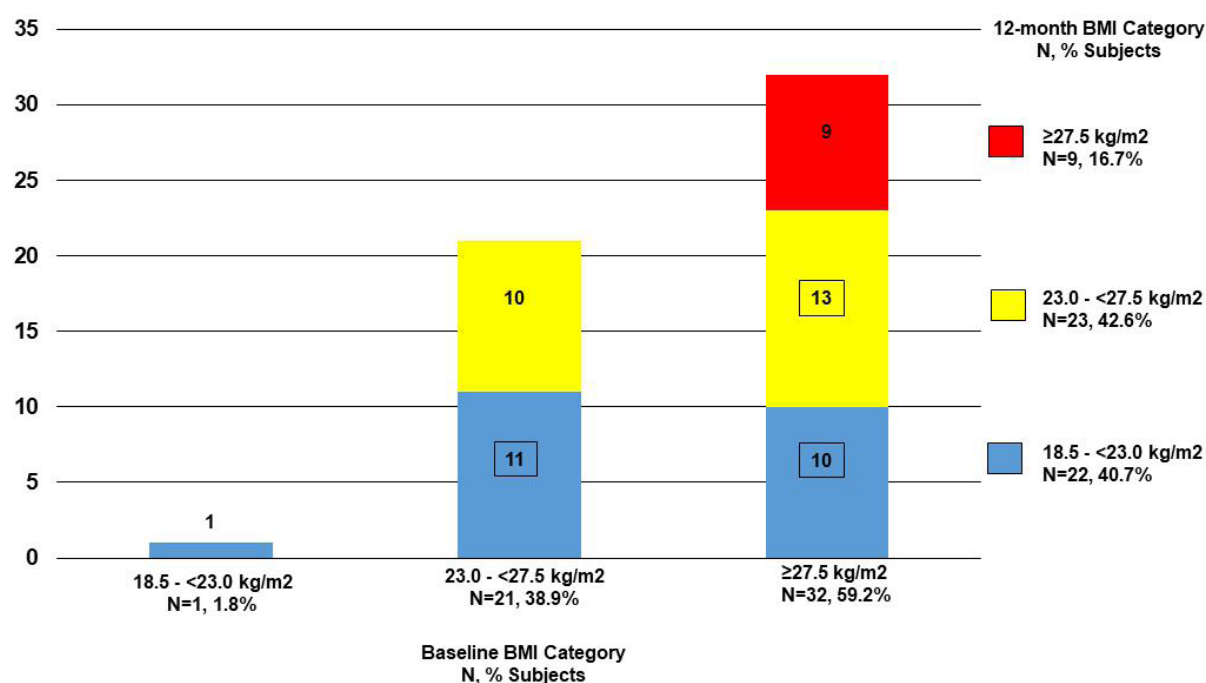


Figure 1. Change in BMI Risk Category after RYGB. The patients with T2DM ($N = 54$) were placed into three groups, dependent on their baseline BMI. The x-axis shows the baseline BMI category distribution, while the y-axis shows the redistribution of the BMI groups at 12 months post-surgery. RYGB: Roux-en-Y gastric bypass; T2DM: type 2 diabetes mellitus; BMI: body mass index.

(19.7%) achieved the defined remission criteria at 12 months after surgery. Preoperative factors in patients with and without T2DM remission were assessed [Table 4]. Univariable analyses identified the age and T2DM duration as being significantly lower and baseline BMI and weight as being significantly higher in the remission group than those in the non-remission group. These findings were confirmed in the multivariable analyses, although the small sample size of subjects with complete data at 12 months limited the generalizability of the results from the regression model.

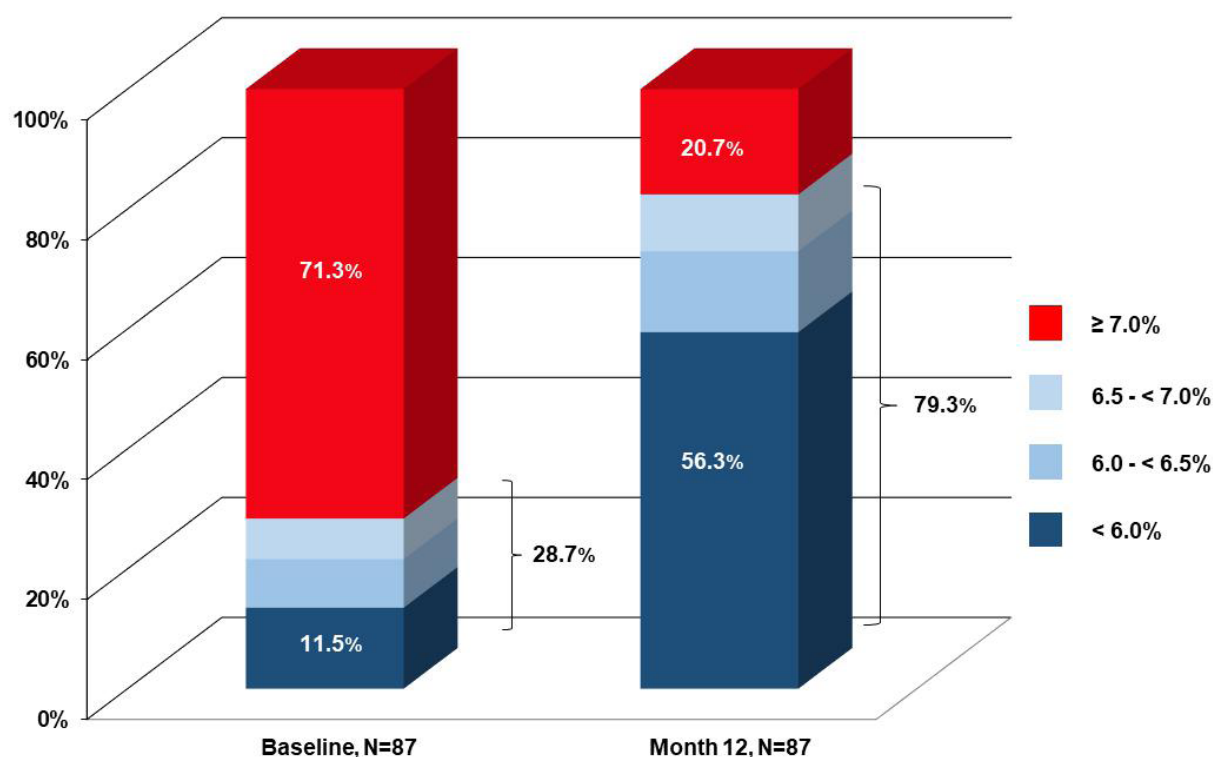


Figure 2. Glycemic control based on HbA1c for patients with T2DM. Patients were separated into four different HbA1c ranges ($N = 87$). The increase in the number of patients under glycemic control ($\text{HbA1c} < 6.0\%$) and the decrease in the number of patients with a high $\text{HbA1c} (\geq 7.0\%)$ are shown. T2DM: Type 2 diabetes mellitus; HbA1c: glycosylated hemoglobin.

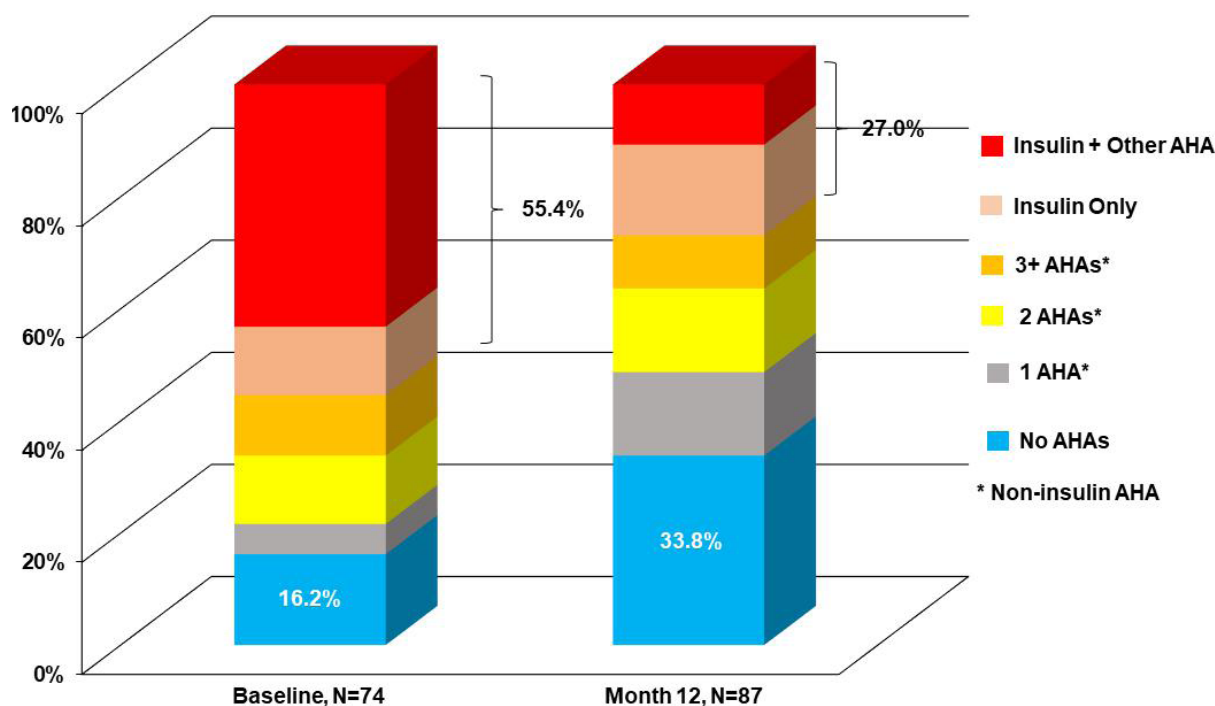


Figure 3. Medication use (anti-hyperglycemic agents) for patients with T2DM ($N = 74$). The decrease in insulin usage is shown. T2DM: Type 2 diabetes mellitus.

Table 4. Univariable analysis of preoperative and postoperative factors in patients with and without T2DM remission

Factor	Remission [†] (n = 14)	No remission (n = 57)	P
Age (years)	37.8 ± 8.4	47.2 ± 9.8	0.002
Weight (kg)	109.3 ± 36.1	86.2 ± 19.8	0.035
BMI (kg/m ²)	36.3 ± 10.1	30.5 ± 6.9	0.013
Waist circumference (cm)	115.6 ± 25.7	102.8 ± 16.6	0.184
Fasting blood glucose (mg/dL)	188.4 ± 77.9	163.8 ± 63.5	0.218
HbA1c (%)	8.6 ± 2.2	7.8 ± 1.9	0.197
Duration of T2DM (years)	3.1 ± 3.6	6.2 ± 4.9	0.030
Number of T2DM medications	1.8 ± 1.9	2.4 ± 1.4	0.249
Weight change (kg)	-25.0 ± 13.2	-18.2 ± 17.2	0.295
Percent weight change (%)	-26.4 ± 10.5	-18.6 ± 13.1	0.123
BMI change (kg/m ²)	-8.4 ± 4.6	-6.6 ± 6.3	0.435

Data are shown as mean ± standard deviation. Results are consistent with the results of multivariable logistic regression, although the sample size was too small to support formal statistical modeling robustly. [†]Remission was defined as fasting blood glucose < 110 mg/dL, HbA1c < 6.0%, and without the use of anti-hyperglycemic agents at 12 months after surgery. BMI: Body mass index; HbA1c: glycosylated hemoglobin; T2DM: type 2 diabetes mellitus.

DISCUSSION

This study showed that RYGB may be effective for weight loss and control of T2DM in Chinese patients who are obese and overweight considering the low remission rate. Patients with T2DM who were younger, had a higher BMI at baseline, and had a shorter T2DM duration were more likely to achieve T2DM remission. In patients with T2DM, significant improvements in anthropometric characteristics were observed at 12 months after surgery. Significant and meaningful improvements were concurrently observed in glycemic and lipid measurements. The outcomes reported in this retrospective study for RYGB appear consistent with recently published literature seen in Western patients with T2DM^[11] and Asian patients with T2DM^[15].

Nevertheless, a major difference should be noted. In Western countries, about 80% of the patients who undergo bariatric surgery are female, mainly because of greater worries about the physical appearance and higher awareness of the impact of overweight on health than men^[16]. In the present study, most patients were male (65%). In the study of the bariatric surgeries performed between 2001 and 2015 in China, Du *et al.*^[5] reported that males represented 48% of the patients, significantly more than in Western countries. The exact reason for this discrepancy is difficult to explain, as highlighted by Du *et al.*^[5], and additional study is necessary.

The WHO has previously presented health action points for BMI categories in Asian populations. The suggested categories were: underweight, < 18.5 kg/m²; increasing but acceptable risk, 18.5-23 kg/m²; increased risk, 23-27.5 kg/m²; and high-risk, ≥ 27.5 kg/m²^[4]. The Diabetes Surgery Summit II (DSS-II) concluded that there is sufficient clinical and mechanistic evidence to support the inclusion of metabolic surgery among antidiabetic interventions for patients with T2DM and obesity, and it should be considered for Asian patients with T2DM and BMI 27.5-32.4 kg/m² if hyperglycemia is inadequately controlled with either oral or injectable medications^[17]. In this study, we found that there was a redistribution of the BMI groups at 12 months after RYGB. In patients in the high-risk category (≥ 27.5 kg/m²) at baseline, risk was reduced by one or more categories in ≥ 70% of patients, and, among those in the increased risk category (23.0 to < 27.5 kg/m²) at baseline, over 50% reached the increasing but acceptable risk category (18.5 to < 23.0 kg/m²). This result is consistent with the conclusions made by the DSS-II.

In the present study, the T2DM remission rate at 12 months was 19.7%, which is lower than that reported in the Swedish Obese Subject study, where the remission rate with surgery was 72.3% at two years, but it decreased to 30.4% at 15 years^[18]. A meta-analysis reported a remission rate of 78.1%^[19]. The exact criteria

for remission and the timing of evaluation may affect the results. In the present study, using strict criteria, remission was observed in 19.7%, but near-remission was observed in the remaining 80.3% of the patients. Of note, LOCF had to be used to account for missing values in many patients.

Nevertheless, this study confirms the results of other work on the effectiveness of RYGB for weight loss in China and contributes to the growing body of evidence that RYGB can slow the progression of weight-related diabetes, even inducing remission in some and improving control with fewer AHAs in the vast majority. Notably, more than half of those on insulin at baseline achieved glycemic control without insulin at 12 months after RYGB surgery. Preventing or reducing the need for insulin treatment is important both from a patient's quality of life perspective and from a healthcare utilization perspective^[20]. In the present study, RYGB allowed at least a partial remission in all patients. Those with a short T2DM duration were at a higher likelihood of achieving remission, while those with a longer duration can nevertheless obtain some benefits from RYGB. Previous studies generally agree that younger age, shorter duration of diabetes, higher C-peptide levels, higher baseline BMI, and higher baseline visceral fat area are associated with remission after surgery^[21-30]. Three prediction models based on different combinations of those variables are available (the DiaRem, ABCD, and individualized metabolic surgery scores)^[21,31-33]. In the present study, no score could be derived from the data because of the limited data, but age and T2DM duration were lower and baseline BMI and weight were higher in the remission group than in the non-remission group, as supported by the previous models^[21,31-33] and studies^[21-30]. Nevertheless, patients with higher BMI at baseline had a higher probability of achieving remission than those with a lower BMI. There is currently no accepted explanation for this phenomenon, but there is the possibility that the disease characteristics (such as insulin resistance and other metabolic disturbances) are different between the two groups of patients^[21]. This will have to be examined using metabolic studies to determine possible differences in energy metabolism among patients that could account for the differences in weight loss. Because the BMI cutoff points are not the same between Chinese and Western patients, it is possible that the percent change in excess weight loss (%EWL) is also different. In the present study, the %EWL was $-42.8\% \pm 44.2\%$, indicating that, although the excess weight was cut by half in most patients, there was a wide variability among patients. In addition, %EWL was not associated with remission, while some previous Western studies associated %EWL with remission^[11,23]. A meta-analysis showed ethnic differences in %EWL after metabolic surgery, although Asian patients were not included^[34]. In addition, around 60% of the patients in this study had a BMI lower than 32.5 kg/m^2 , which may be very different from Western populations.

In the present study, the operative time and length of stay were longer than those usually observed in Western countries. The present study covered the 2009-2014 period, and Du *et al.*^[5] showed that, even though bariatric surgery has been performed in China since 2001, most of the cases were in the 2011-2015 period, suggesting that the experience during 2009-2014 was relatively low, leading to longer surgeries. Regarding the length of stay, there is a shortage of general practitioners in China, and the Chinese healthcare system is based on specialists^[35]. Therefore, patients are generally discharged when all symptoms and signs are resolved, leading to longer lengths of stay.

STRENGTHS AND LIMITATIONS

The strength of this report is the multicenter approach of data collection, capturing data from five Chinese hospitals. This report provides one of a limited number of multicenter studies available from China^[12]. This study has several limitations, including the retrospective design, no comparative arm, a single procedure (RYGB) evaluated, exclusion of patients without 12-month data, a small patient population, lack of complete outcome data reported on the majority of patients at 12 months (e.g, BMI values were only available in 78 out of 103 T2DM subjects), and the short-term follow-up. The data were from the first sites in China that conducted RYGB surgery, and it took time for patients to accept the new treatment pathway.

Further work in prospective, multicenter, long-term follow-up designed studies is warranted to support RYGB as an effective, long-lasting treatment option in both morbidly and non-morbidly obese Chinese patients with T2DM.

In conclusion, This study supplements the evidence showing that RYGB is an important surgical option for the control of obesity and weight-related T2DM in Chinese patients. Half of the patients with insulin requirements at the time of RYGB can expect to maintain glycemic control with non-insulin AHAs after RYGB. Those not taking insulin prior to RYGB can expect to achieve glycemic control with fewer AHAs, and, if a patient has a short T2DM duration, glycemic control can even be achieved without the need for AHAs.

DECLARATIONS

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Authors' contributions

Execution, data collection and interpretation, manuscript preparation, and final approval: Yang W

Execution, data collection, and manuscript review and final approval: Zhu S, Cheng Z, Zhang N, Wu L, Chen Y, Yang J, Yu S

Clinical study design, data interpretation, and manuscript review and final approval: Yang TF, Ding D

Clinical study design, data interpretation, manuscript preparation, and final approval: Waggoner JR

Clinical study design, data interpretation, manuscript review and final approval: Schwiers ML, Fegelman EJ

Execution, data collection and interpretation, and manuscript review and final approval: Wang CC

Availability of data and materials

Not applicable.

Financial support and sponsorship

Funding for this study has been provided by Ethicon Endo-Surgery, Inc.

Conflicts of interest

Yang W, Zhu S, Cheng Z, Zhang N, Wu L, Chen L, Yang J, Yu S, Wang CC declare that they have no conflict of interest. Yang TF and Ding D are employed by Johnson & Johnson Medical (Shanghai) LTD. Waggoner JR, Schwiers ML and Fegelman EJ are employed by Ethicon Endo-Surgery, Inc.

Ethical approval and consent to participate

This study was approved by the Ethical Committee of the First Affiliated Hospital of Jinan University, Guangzhou, China. It also was registered on the Chinese Clinical Trial Registry website (www.chictr.org.cn) with Registration Number: ChiCTR-OOC-15006387.

Consent for publication

Not applicable.

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Editorial

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Robotic surgery: is it really different from laparoscopy? a critical view from a robotic pioneer

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I got involved in robotic surgery more than 25 years ago, with the development of our own robotic arm, as an assistant holder for the laparoscope, the first Canadian laparoscopic robotic arm, a vertical like AESOP laparoscope holder^[1]. It was built by using an industrial robotic arm from CRS Robotics corporation (Burlington Ontario) used in automated labs, transformed with the help of engineers from the Polytechnique of Montreal of the University of Montreal, and eventually added the first voice activation from Northern Telecom, before Computer Motion's HERMES system^[2]. However, it was never commercialised, and I started to work at the Cleveland clinic in mid-1995, working in partnership with Computer Motion for the clinical developments of the ZEUS robotic system. One of the first concepts of using robotic systems for surgery was the parallel credence of the employment of “master-slave” manipulators used in the nuclear industry for the handling of deadly radiation materials. Hence, I visited at the invitation and organisation of the late Prof. Gerard Buess the “master-slave” manipulator installed at the Karlsruhe Nuclear Research Center, in Karlsruhe Germany^[3]. This consisted of a seat with hand holding large crude manipulators, watching through a window, two arms picking up radiation containers, and then a crude template for a “robotic system” for surgery.

At the headquarters of Computer Motion in Goleta California, I was the very first to demonstrate a complete robotic-assisted mammary-coronary anastomosis in the porcine model, demonstrating the true potential of robotic surgery. My experience in 1995-1997 led us to believe that robotic systems were especially made for small anastomosis, by having the first ZEUS system ever built, at the Cleveland clinic in 1996, after convincing the legendary CEO Dr. Floyd Loop, a cardiac surgeon himself, who got



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interested in the technology for future cardiac applications. I had worked previously with Dr. Gilles Soulez back at the Hotel-Dieu de Montreal, an interventional radiologist, on a percutaneous guided mammary-coronary anastomosis, under thoracoscopic guidance, and had experimented with thoracoscopic coronary anastomosis in the swine before 1995^[4]. This led to animal and clinical trials at the Cleveland clinic with small calibre anastomosis like the coronary anastomosis and fallopian tube reconstruction^[5-7]. I then moved to Mount Sinai School of Medicine in New York in 1998, leading the laparoscopic and bariatric surgery section, and convinced Larry Hollier, the new chairman of the surgery, to get a lease on ZEUS. After also convincing Jacques Marescaux from IRCAD to acquire the same model ZEUS, as he did not want initially, so we could perform using the same system, a surgery between New York and Strasbourg, rather than the incompatible DaVinci at the time, to perform the first transatlantic robotic assisted surgery^[8]. ZEUS had been used first for human coronary and cardiac applications, and gynecological applications, but DaVinci got there first in human general surgical applications^[9-11]. Both had their strengths and weaknesses, and for the next 5 years, conferences were presenting clinical work from those 2 systems. Thus, after the collapse of Computer Motion due to losing a major key patent lawsuit with Intuitive Surgical, and their merger in 2003, my development efforts with robotic surgery were halted. The lack of competition for the next 15 years, led Intuitive to occupy the field alone, and frankly with slow improvements on the existing system of the 1990'S. For me, it didn't make sense to perform large suture surgeries (2-0 and 3-0) with those systems, as we demonstrated already in 1996, the equivalence of laparoscopic surgery, at much lower costs^[12]. We even did a comparison with the 2 existing robotic systems ZEUS vs. DaVinci, and laparoscopic surgery, showing no real differences and advantages^[13]. One difficulty in comparing laparoscopic surgery and robotic surgery is the added 3D vision with robotic surgery, and one had to wonder if we are really comparing surgical systems or visual systems, as comparison between 2D and 3D systems in laparoscopic surgery has shown an advantage for non-experience or poorer proficient surgeons^[14,15]. It seems to me that this is what is captured in the comparison of robotic vs. laparoscopic surgery using the existing system, mostly a 3D effect.

Both the Zeus system and the DaVinci system are not a true robotic system, but rather a “master-slave” manipulator as used in the nuclear research facilities. Hence, whatever you do with the manipulator, it is reproduced with fidelity and filtered at the end of the “slave” instrument, or “garbage in, garbage out”. Hence, if the surgical gesture is excellent, the surgery will be excellent; if it is bad, the surgery will not be corrected into a good one, due to the lack of artificial intelligence. Also, as Dr. Harvey Cushing, one of Harvard's great neurosurgeons, once remarked, “There is no such thing as minor surgery, but there are a lot of minor surgeons.”, and robotic assisted surgery still requires skilled hands^[16]. Therefore, from that perspective, what people call “robotic surgery”, is actually laparoscopic surgery with surgical human hands, period. I continued in the early 2000's at Mount Sinai School of medicine to dabble with the DaVinci robot looking for general surgical applications, especially in bariatric surgery, because it was there in the corner accumulating dust^[17,18]. I did not find it useful, and it was slower for me, taking more time to set up the operating room, and not providing any clinical benefit to patients.

After several clinical series have been published on the matter of robotic-assisted surgery for general surgery, HPB surgery, thoracic surgery, urology, gynaecology and now other surgical fields, RCT (Randomized Controlled Trial) data followed this period comparing robotic surgery to laparoscopy, but also later between robotic surgery and open surgery. Most trials have shown no difference clinically, between laparoscopic surgery and robotic surgery^[19-28]. Why then robotic-assisted surgery vs. open surgery? Because if you cannot demonstrate a clinical benefit with laparoscopic surgery, then those who sell the system, will use arguments that it does have benefits over open surgery. However, we already demonstrated this in the 1990s, where laparoscopic was demonstrated to be superior in decreasing length of stay, pain, morbidity and mortality, as well as costs. So why repeat it? Perhaps because it is the only argument left, trying to confirm to the users and patients that robotic surgery is giving benefits on its own. The robotic

industry has never been able to demonstrate a cost advantage to laparoscopic surgery, and it will get worse. Why? Because the cost of doing laparoscopy is constantly decreasing, year after year, with cheaper trocars and better staplers, and more solid reusables of increasing quality. While regarding robotic-assisted surgery at the moment, costs are increasing year after year, with cost of research and development having to be amortized in the costs of robotic systems, costs like disposables, added energy sources, stapling and approximation technologies and perhaps in the near future, artificial intelligence and image processing. Also, diameters are getting smaller, and more endoscopic tools are getting into play so that the combination of laparoscopic and flexible endoscopy may give a hard time to robotic systems in the next 2 decades at a lower cost again. If patients can be discharged the same day, it will be difficult to beat, as costs will be even lower. It may also be a generation thing^[29]. The younger surgical generation has not known the struggles and fights to move laparoscopy from open surgery. They have been raised with computer games, laptops, and smartphones. They see robotic-assisted surgery as a similar platform and learn it faster than training harder with discipline on laparoscopic instruments, even if it costs more at the end, I think. There is the promise that true robotic surgery will emerge one day, so they might get involved now after all.

Then do you know what robotic-assisted surgery really is or should be^[30]? It is autonomous surgery with artificial intelligence. The presently called “robotic surgery” is not, which is a misnomer, a confused terminology, as it is firstly laparoscopic-assisted, and the robot is not a robot. The early pioneers of so-called robotic surgery, are today not doing any sort of routine or daily robotic surgery, who long ago saw no real benefit of the technology. Ask Jacques Himpens and Guy-Bernard Cadiere from Belgium, the first users of the DaVinci, and myself the first user of Zeus. We are not doing any sort of regular robotic surgeries. We did not get fooled by these laparoscopic manipulators; we have been waiting for the real thing for 25 years now. I did work on the clinical development of Surgibot (different from Senhance, Surgibot is a flexible single port platform) from Trensenterix, a North Carolina based company, and provided animal expertise and data for the FDA approval, but the robot did not demonstrate superiority to existing laparoscopy, and the approval was denied in 2016. Transenterix sold the intellectual property to GBIL(Great Belief International Limited) in December 2017 for 29 millions, with the hope to develop it in China. GBIL also acquired Auto-Lap in 2019, reminiscent of AESOP reinvented, a laparoscope holder, as we are now closing the circle 25 years later. How interesting! Now that the general robotic surgical patents have expired, and there are a multitude of copycats like, competition is finally happening again, we may see emerging real robotic surgery, and until then, it is not different from laparoscopic surgery.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

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The author 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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Review

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Minimally invasive glaucoma surgery - current and emerging techniques to reduce intraocular pressure and medications

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Abstract

Minimally invasive glaucoma surgery (MIGS) has become increasingly popular as a step in the management pathway of open angle glaucoma. Due to the relative novelty of these devices, there remains some paucity of evidence relating to their long-term efficacy and safety, and this can make comparison between these techniques somewhat complex. This review article aims to guide clinical decision making by providing the latest evidence on the comparative efficacy of current iterations of minimally invasive glaucoma surgery. A literature review was conducted to identify the most significant recent evidence to support the safety and efficacy of the various forms of minimally invasive glaucoma surgery. Included studies provided efficacy and safety data on a variety of minimally invasive glaucoma surgery methods. The PubMed database was searched and a total of 484 studies, published between 2015 and 2020 were identified, of which 27 were included. The studies indicate that most available forms of minimally invasive glaucoma surgery show statistically significant efficacy in terms of intraocular pressure reduction and improvement in medication burden, while maintaining an acceptable safety profile.

Keywords: Minimally invasive glaucoma surgery, open angle glaucoma, trabecular microbypass, ab-interno canaloplasty, trabeculectomy, suprachoroidal, subconjunctival



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INTRODUCTION

Minimally invasive glaucoma surgery (MIGS) is an emerging field in open angle glaucoma (OAG) management with a promise to offer a reduction in intra-ocular pressure (IOP) and medication burden without the comparatively high risk of complications associated with more invasive incisional procedures. Glaucoma is characterized by progressive optic neuropathy that is associated with progressive field loss in which IOP is a key modifiable factor. Current established management options to reduce IOP primarily revolve around topical medications or application of selective laser trabeculoplasty (SLT) or a combination of both. Failing these, patients will often require invasive and complicated surgery to avoid blindness. In recent years, however, MIGS has heralded a new dawn in reducing IOP for glaucoma patients.

Topical medications for glaucoma

The main aim of topical therapy is to reduce IOP and to do so with fewer medications and side effects as possible (summarised below in [Table 1](#) in order of treatment preference)^[1]. The first-line topical agents in OAG are the prostaglandin analogues, which utilise the uveoscleral pathway to increase outflow of aqueous humor and are usually taken as a single dose at night. These medications cause minimal systemic adverse events, but local adverse events including conjunctival hyperaemia, periocular darkening, iris darkening, eyelash darkening and lengthening, macular oedema, and uveitis are known to occur. Second-line agents include β -adrenergic blockers, α -agonists, carbonic anhydrase inhibitors, and cholinergic agonists, and are used when prostaglandin analogues are insufficient to control IOP or are contraindicated. Many of these medications cause local and systemic side effects including ocular irritation and dry eye. β -adrenergic blockers in particular are contraindicated in chronic obstructive pulmonary disease, asthma and bradycardia due to their systemic effects^[1].

Alternatives to topical medications

While medications can significantly reduce the disease progression of OAG with ideal use, they are limited by inconsistent compliance and their associated side effect profile. Compliance can be affected by a multiplicity of medications and long duration of treatment. A recent study of 128 South Australian patients found that for patients on long-term topical glaucoma therapy, the maximal adherence level was as low as 41.4%. The primary reason for poor compliance was reported as poor memory or forgetfulness^[2]. For this reason, medications are often inferior to surgical intervention as they require long-term compliance, and in this case only an estimated 41.4% of patients are truly seeing the full effect of treatment, in comparison with surgery where ongoing effect is not reliant on the patient's ability to comply with the treatment regimen.

For severe OAG that is uncontrolled with medications, trabeculectomy is the most common IOP-lowering surgery performed; however, it is an invasive procedure and carries a significant risk of complications. A recent Cochrane review of five studies showed that complications are comparatively likely with trabeculectomy. These include hyphaema (seen in 13.1% of eyes), shallow anterior chamber (14.1%), choroidal detachment (14.1%), postoperative IOP spike (2.1%), anterior chamber inflammation (7.3%), hypotony (15.6%) and accelerated cataract progression (13.7%)^[3]. An alternative to trabeculectomy is laser trabeculoplasty, which is a less invasive in-office procedure that can lead to significant IOP reductions; however, it is less effective than undergoing a trabeculectomy, with a 10% failure rate per year^[1]. In addition to these methods, whilst cataract surgery is traditionally performed to treat vision distortion, it is also a proven effective adjunct in the management of glaucoma. Phacoemulsification alone has been shown to cause a mean reduction in IOP of 5.3 ± 3.9 mmHg and reduce mean medication burden from 1.7 ± 0.9 to 0.7 ± 0.9 at 24 months as a standalone procedure^[4].

What is minimally invasive glaucoma surgery?

Given the limited success profile of current treatments, MIGS has become increasingly popular as a form of treatment for glaucoma. There are numerous MIGS approaches, including: (1) increasing flow through the

Table 1. Summary of current medical glaucoma treatment

Medication class	Examples	Mode of action	Adverse effects	Precautions
Prostaglandin analogues	Travoprost Bimatoprost Latanoprost Tafluprost Unoprostone	Increasing uveoscleral outflow of aqueous humour	Iris hyperpigmentation Darkening/discolouration lid/conjunctival oedema Uveitis or iritis Macular oedema	Iritis/uveitis Herpetic keratitis Aphakia Pregnancy
β -adrenergic blockers	Timolol Betaxolol Carteolol Metipranolol Levubunolol	Suppress aqueous humour production	Blurred vision Stinging Bradycardia	Systemic beta blockade Asthma COPD Bradyarrhythmia
α -adrenergic agonists	Apraclonidine Brominidine	Suppress aqueous humour production and increased uveoscleral outflow	Ocular allergy Hyperaemia Ocular irritation Dry mouth and nose Taste disturbance Headache	Severe cardiovascular disease
Carbonic anhydrase inhibitors	Brinzolamide Dorzolamide Acetazolamide	Suppress aqueous humor production	Ocular irritation Transient blurred vision Foreign body sensation Bitter taste	Compromised corneal endothelium Pregnancy
Cholinergic agonists	Pilocarpine Carbachol	Increased trabecular aqueous humour outflow	Blurred vision Myopia Ocular irritation Headache	Uveitis Iritis Risk of retinal detachment Heavily pigmented eyes

Summary of current glaucoma medications in descending order of treatment preference. COPD: Chronic obstructive pulmonary disease^[1].

trabecular meshwork and Schlemm's canal; (2) directing flow through the supraciliary space; (3) directing aqueous outflow to the subconjunctival space; and (4) reducing the production of aqueous fluid at the ciliary processes.

All of these methods share some common features including an ab-interno approach which spares incision of the sclera, leading to a more favourable side effect profile compared with some other traditional pressure lowering procedures such as trabeculectomy or ab-externo drainage devices. However, one important distinction is that MIGS generally leads to a smaller reduction in intra-ocular pressure than more invasive approaches, and for this reason it is important to consider the individual patient needs prior to deciding upon the glaucoma management.

In this study a literature review was performed, assessing the different types of MIGS procedures and providing an overview of their comparable efficacy in an effort to inform clinical decision making and bring attention to the variety of MIGS available.

METHODS

A literature review was performed to identify studies that evaluated the efficacy and safety of various MIGS procedures. For the purposes of this review, included studies had to provide data on currently available forms of MIGS in terms of IOP and medication reductions, and also comment on the safety profile of these devices. In the case of emerging MIGS, studies were included if they gave a description of these devices or included a description of upcoming trials. Exclusion criteria included non-English language papers, non-human research, case studies and articles written before the 1st of January 2015.

The electronic database used for this literature review was PubMed. The database was searched in October 2020. The search was limited to articles published from January 1, 2015 to October 9, 2020 in the English language. The search terms were: [(MIGS OR micro invasive OR micro bypass OR stent) AND (glaucoma

Table 2. Summary of efficacy results from studies included in the review

Technique	Study	Combination/ standalone	Study design	Population	IOP change (%)	Medication reduction
Schlemm's canal						
iStent	Hooshmand <i>et al.</i> ^[5]	+ CE	PCS	245 eyes	18 mo: -13.23	18 mo: -0.8
	Ferguson <i>et al.</i> ^[6]	+ CE	RCS	24 eyes	36 mo: -24.72	36 mo: -0.16
	Ferguson <i>et al.</i> ^[7]	+ CE	RCS	115 eyes	24 mo: -27.45	24 mo: -0.7
	Ahmed <i>et al.</i> ^[8]	+ CE	RCT	75 eyes	12 mo: -5.24	12 mo: -1.0
	Katz <i>et al.</i> ^[9]	Standalone	RCT	119 subjects	42 mo: -21.89	42 mo: -1.65
iStent inject	Hooshmand <i>et al.</i> ^[5]	+ CE	PCS	245 eyes	18 mo: -11.64	18 mo: -0.8
	Samuelson <i>et al.</i> ^[10]	+ CE	RCT	505 eyes	24 mo: -40	24 mo: -1.2
Hydrus	Samuelson <i>et al.</i> ^[4]	+ CE	RCT	556 eyes	24 mo: -43.68	24 mo: -1.4
	Ahmed <i>et al.</i> ^[8]	+ CE	RCT	73 eyes	12 mo: -8.95	12 mo: -1.6
ABiC	Davids <i>et al.</i> ^[11]	+/- CE	RCS	36 eyes	12 mo: -30.3	12 mo: -0.37
	Heersink <i>et al.</i> ^[12]	+ CE + iStent	RCS	86 eyes	6 mo: -17.47	6 mo: -0.9
Trabectome	Esfandiari <i>et al.</i> ^[13]	+ CE	RCS	154 eyes	24 mo: -9.15	24 mo: -0.6
	Avar <i>et al.</i> ^[14]	+/- CE	RCS	154 eyes	60 mo: -25.22	60 mo: -1.3
GATT	Olgun <i>et al.</i> ^[15]	+/- CE	RCS	107 eyes	24 mo: -38.55	24 mo: -2.1
Goniotomy	Elmallah <i>et al.</i> ^[16]	+ CE	RCS	315 eyes	12 mo: -27.47	12 mo: -1.03
Supraciliary space/ciliary process						
CyPass	Vold <i>et al.</i> ^[17]	+ CE	RCT	374 subjects	24 mo: -30.33	24 mo: -1.2
	Reiss <i>et al.</i> ^[18]	+ CE	RCT	215 subjects	60 mo: -34.29	n/a
	Fard <i>et al.</i> ^[19]	+ CE	SR/MA	274 subjects	24 mo: -35.7	24 mo: -0.66
	Fard <i>et al.</i> ^[19]	Standalone	SR/MA	182 subjects	24 mo: -16.1	24 mo: -1.24
iStent Supra	Myers <i>et al.</i> ^[20]	+ 2 iStent	PCS	80 subjects	48 mo: -41.36	n/a
ECP	Pantaloni <i>et al.</i> ^[21]	+ CE + 2 iStent	PCS	63 eyes	12 mo: -34.65	12 mo: -0.98
Subconjunctival space						
XEN Gel Stent	Olgun <i>et al.</i> ^[15]	+/- CE	RCS	114 eyes	24 mo: -41.8	24 mo: -2
	Karimi <i>et al.</i> ^[22]	+/- CE	RCS	226 subjects	18 mo: -30.05	18 mo: -1.5
	Wagner <i>et al.</i> ^[23]	Standalone	RCS	171 eyes	12 mo: -37.89	12 mo: -1.7
	Gillmann <i>et al.</i> ^[24]	+/- CE	PCS	110 eyes	24 mo: -27.53	24 mo: -1.45
MicroShunt	Sadrudin <i>et al.</i> ^[25]	+/- CE	RA	23 patients	36 mo: -44.96	36 mo: -1.7

CE: Cataract extraction; PCS: prospective case series; RCS: retrospective case series; RCT: randomised controlled trial; SR/MA: systematic review and meta-analysis; RA: review article.

OR trabecular)]. After this, 2 reviewers (K.K. and P.R.) independently screened the retrieved records to identify eligible studies with discrepancies resolved by discussion. The reference lists of the searched studies were also analysed to identify any suitable papers that were not identified by the search. The initial screening was performed based on title and abstract for relevance, with subsequent in-depth screenings based on full-text analysis. The 2 reviewers (K.K. and P.R.) then selected the most significant articles for each MIGS technique from the eligible studies for inclusion, based on a ranking criteria, prioritising studies on the strength of their design, recency, and the size of the study.

RESULTS

Description of included trials

484 papers were identified from the literature search. The abstracts of these papers were screened by 2 authors. 8 papers were excluded as duplicates, and 313 were excluded for not meeting the inclusion criteria, 163 papers were selected as relevant based on the specified search criteria. Using these relevant articles, 2 authors independently prepared a list of the most significant publications for each MIGS technique based on study size, recency and strength of the study design. After cross-referencing both lists, the 2 authors reached a consensus as to the articles which would be included in the review, and this decision was reviewed by senior authors. After resolving discrepancies in the lists, 25 studies were finally included in the review (details listed comprehensively in [Supplementary Table 1](#)).

Key statistics on mechanism of action, effectiveness, and safety profile were extracted for each type of MIGS (an overview of these findings summarised in [Table 2](#)). Analysed procedures were limited to

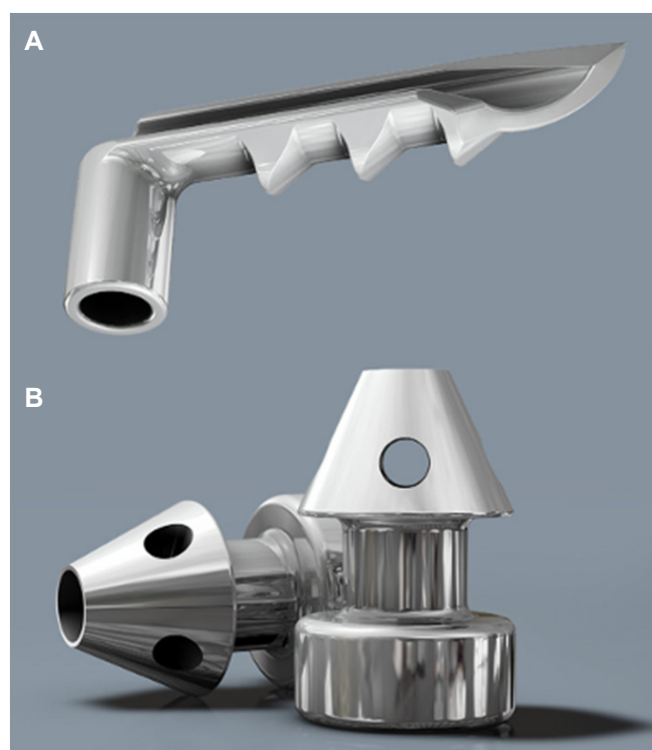


Figure 1. First generation iStent trabecular microbypass stent (A). Second generation iStent inject trabecular microbypass stent (B). This figure is quoted with permission from Hooshmand et al.^[5].

MIGS procedures that have a reasonable evidence base. MIGS approaches that were identified include: iStent, iStent inject, Hydrus, Ab-interno Canaloplasty, Trabectome, CyPass, iStent Supra, Xen, Preserflo microshunt, Endocyclophotocoagulation, SLT and the emerging MIGS including MINiject, Beacon Aqueous Microshunt and the extended-release drug delivery systems.

THE DIFFERENT TYPES OF MIGS APPROACHES

Including mechanism of action, effectiveness, and safety profile.

MIGS aimed at improving outflow through Schlemm's canal

iStent and iStent inject: Mechanism of action

The iStent and iStent inject (Glaukos Inc, Laguna Hills, CA, USA) are first and second generation trabecular microbypass stents, aimed at improving outflow of aqueous humor through the trabecular meshwork into Schlemm's canal (both pictured in Figure 1)^[5]. Both are made of heparin coated titanium, and while the iStent is 1 mm × 0.3 mm in size, the iStent inject is significantly smaller at only 360 μm × 230 μm in size. Both are inserted using a disposable implantation device through a clear corneal incision as a single procedure or in combination with cataract extraction, and in the case of iStent inject 2 devices are loaded into the injector and can be placed at 30°-60° apart. Both devices are usually followed up with a 4-week course of topical anti-inflammatory and anti-infective medication to reduce the risk of surgical complications^[26]. Generally, iStent or iStent inject is indicated in mild to moderate glaucoma with the aim to reduce dependence on topical medications and/or to reduce IOP. These trabecular microbypass devices have an advantage in that they are very small devices, and so are unlikely to cause endothelial damage in patients with shallow anterior chambers.

iStent and iStent inject: Effectiveness

Hooshmand *et al.*^[5] found that iStent and iStent inject (both combined with phacoemulsification) had comparable effectiveness in practice, with their study of 145 eyes with primary OAG showing 56.0% of the iStent and 51.3% of the iStent inject eyes achieved an IOP value of ≤ 18 mmHg and were medication free at 12 months. In a randomised prospective trial conducted by Samuelson *et al.*^[10], iStent inject with phacoemulsification was compared with phacoemulsification alone in terms of safety and efficacy. The proportion of eyes that had achieved an IOP reduction of $\geq 20\%$ from baseline at 24-month follow-up was 75.8% in treatment eyes compared with 61.9% of eyes in the control group. 84% of treatment eyes compared with 67% of control eyes were medication free at the 23-month follow-up^[10].

It has also been demonstrated in an RCT by Katz *et al.*^[9] that increasing the number of iStent devices implanted as a standalone procedure leads to an increased treatment effect. Whilst all patients in this trial were taking between one to three topical medications pre-implantation, all were taken off post-operatively, and in the 1-iStent group 18/38 participants required the addition of a topical medication by 42 months, compared with 4/41 in the 2-iStent group and 3/40 in the 3-iStent group^[9].

iStent trabecular microbypass devices have also demonstrated efficacy in secondary OAG. In one 24-eye study of iStent in combination with phacoemulsification in pigmentary glaucoma there was a reduction in IOP from 19.50 ± 6.7 mmHg at baseline to 14.68 ± 3.0 mmHg ($P < 0.01$) at 36 months in addition to a reduction in medications from 0.75 ± 1.0 topical medications to 0.59 ± 0.6 ($P > 0.05$)^[6]. Pseudoexfoliation glaucoma was also investigated by Ferguson *et al.*^[7], with iStent implantation in combination with phacoemulsification in 115 eyes leading to a statistically significant reduction in mean IOP and topical medication usage at 2 years. No studies were identified that solely investigated iStent or iStent inject in steroid induced glaucoma.

iStent and iStent inject: Safety profile

Samuelson *et al.*^[10] reported the overall adverse events to be less frequent in the intervention group who received iStent and phacoemulsification (54.1%) vs. the control group (who only received cataract extraction) (62.2%), and the majority of these were minor complications, the most common being ocular surface disease, stent obstruction, intraocular inflammation, secondary surgical inflammation and ocular allergies. Of those who had stent obstruction ($n = 24$), 3 had a laser revision to clear the blockage and these were all successful^[10].

Hydrus: Mechanism of action and effectiveness

The Hydrus microstent (Ivantis inc, Irvine, CA, USA) is an 8-mm intracanalicular scaffold that dilates an entire 90° quadrant of Schlemm's canal to increase aqueous humor flow through the trabecular meshwork (displayed in [Figures 2 and 3](#)). The Hydrus implant is introduced in a fashion similar to other trabecular microbypass stents, through a clear corneal incision with phacoemulsification or as a single procedure, and with the application of a topical corticosteroid and antibiotic solution during the post-operative period. The indication for Hydrus is mild to moderate glaucoma with the aim of reducing dependence on topical medication and to control IOP within a suitable target^[26].

The efficacy of Hydrus in combination with phacoemulsification compared to phacoemulsification alone was investigated in the recent HORIZON study by Samuelson *et al.* In this 369-eye study, an unmedicated IOP reduction of $> 20\%$ was achieved in 77.3% of Hydrus eyes compared with 57.8% of control eyes at 24 months. There was a mean reduction of 7.6 ± 4.1 mmHg in the Hydrus group and 5.3 ± 3.9 mmHg in the phacoemulsification alone group. Mean medication burden was reduced from 1.7 ± 0.9 pre-operatively (baseline value in both intervention and control was equivalent) to 0.3 ± 0.8 in the Hydrus group and to 0.7 ± 0.9 in the phacoemulsification alone group^[4].

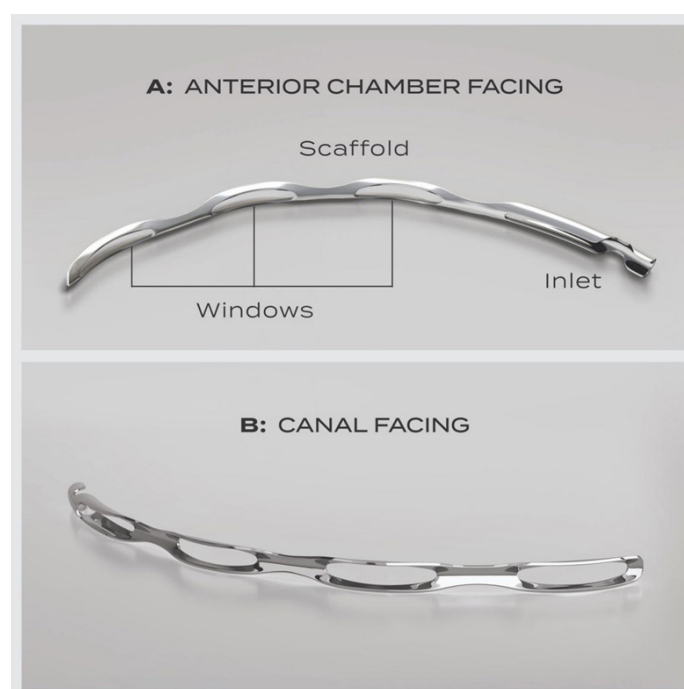


Figure 2. Hydrus microstent (Ivantis inc, Irvine, CA, USA). (A) diagram of the Hydrus microbypass stent with the anterior chamber forward. (B) is an image of the posterior chamber. Image copyright of Ivantis, Inc.

Hydrus was also investigated as a head-to-head comparison with 2 first-generation iStent (both performed following uncomplicated cataract surgery) in the COMPARE trial, a 152-patient randomised clinical trial by Ahmed *et al.*^[8] It was concluded in this study that Hydrus reduced IOP at 12 months by 1.7 ± 4.0 mmHg compared with a reduction of 1.0 ± 4.0 mmHg in the 2-iStent group, a difference of 0.7 mmHg (95%CI: -2.0-0.7). Medication reduction was also greater as Hydrus achieved a reduction of 1.6 ± 1.2 medications vs. 1.0 ± 1.2 in the 2-iStent group, a difference in 0.6 medications (95%CI: 0.9-0.2). Interestingly, Hydrus was able to achieve a $\geq 20\%$ IOP improvement in 39.7% of patients compared with only 13.3% in the 2-iStent group and was able to achieve 30.1% in the ≤ 18 mmHg category compared with only 9.3% in the 2-iStent group^[8].

Hydrus: Safety profile

Adverse events were roughly comparable between both of the groups in the COMPARE trial in terms of BCVA loss, IOP spikes, new cataracts and device obstruction. 2 patients in the Hydrus ($n = 74$) and 1 in the 2-iStent ($n = 76$) experienced a BCVA loss of > 2 lines at 12 months, and IOP spikes of > 10 mmHg were seen in 3 patients in the Hydrus group and 4 patients in the 2-iStent group. New cataracts were seen in 2 patients in the Hydrus group and in 1 patient in the 2-iStent group and device obstruction due to any cause was seen in 9 of the Hydrus and 10 of the 2-iStent patients.

Safety of the Hydrus microstent was generally reflective of the safety of other trabecular microbypass devices. There was also no need for any incisional glaucoma surgery in the Hydrus group compared with in the 2-iStent group, where 2 patients (of 76 in that group) required a secondary trabeculectomy and 1 patient required a cataract surgery^[8].

Ab-interno canaloplasty: Mechanism of action and efficacy

Ab-interno canaloplasty (ABiC) is a procedure where a microcatheter such as the iTrack device (Ellex Medical Lasers Pty Ltd, Adelaide, Australia) is used to perform 360° viscodilation of Schlemm's canal,

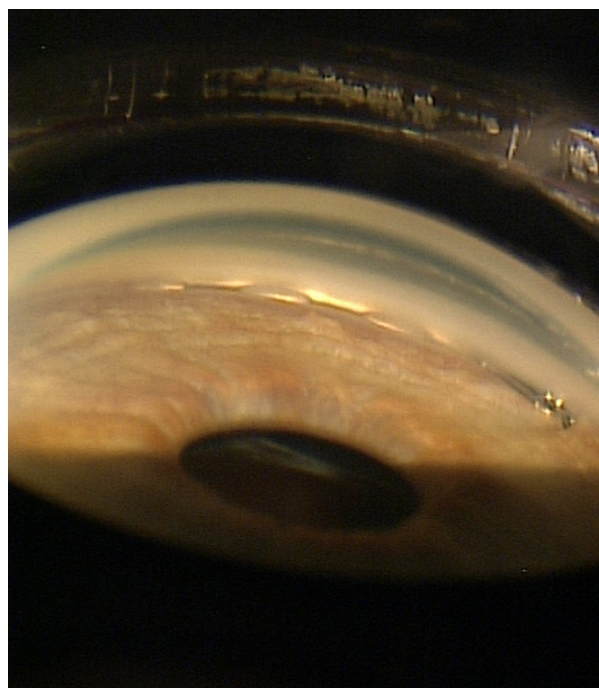


Figure 3. Hydrus microstent (Ivantis inc, Irvine, CA, USA) viewed gonioscopically in position in the canal of Schlemm. The device is partially obscured by the overlying trabecular meshwork. Image copyright of Ivantis, Inc.

without the requirement for suturing. This acts to reduce IOP by dilating the canal of Schlemm and downstream collector channels to improve aqueous outflow. The indication for ABiC in mild to moderate glaucoma is either as a solo procedure or in combination with other forms of trabecular microbypass devices to facilitate further dilation of the collecting channels, and greater outflow than would be achieved with these devices alone, a similar principle to other non-implantation techniques specifically targeting improved outflow through Schlemm's canal.

ABiC has been evaluated as both a sole procedure in phakic eyes and in combination with cataract surgery by Davids *et al.*^[11] In one study of 36 eyes (20 pseudophakic and 16 phakic) a reduction in mean IOP was seen from 19.8 ± 4.1 mmHg pre-operatively to 13.8 ± 3 mmHg 12 months post-operatively across the 2 groups^[11]. There was, however, no statistically significant reduction in the number of medications during this period, which stabilised at 2.1 ± 1.6 ($P = 1.0$). This would be an important point to include when counselling patients about ABiC as a sole procedure^[11].

ABiC also has the potential to be used as a combination therapy with other forms of MIGS. Heersink *et al.*^[12] explored this concept in their 186-eye retrospective study comparing iStent and cataract surgery with iStent, ABiC and cataract surgery. The results showed a clear favourability for the IOP lowering effects of iStent with ABiC and phacoemulsification, as this group achieved a mean IOP reduction of 2.9 ± 3.6 mmHg compared with 1.7 ± 3.1 mmHg in the iStent and phacoemulsification groups alone. The percentage of patients achieving treatment success (a final IOP of ≤ 18 mmHg and a mean reduction in IOP of $> 20\%$) was 46% in the combined group compared with 35% in the trabecular microbypass and cataract surgery alone group. In terms of medication, 56% of patients in the combined group were off all medications compared with 48% in the control group, a mean reduction of 0.9 and 0.7, respectively^[12].

It is likely that ABiC would be an effective procedure to combine with existing trabecular microbypass methods. As a sole procedure it is also effective at lowering IOP; however, it has showed limited efficacy in

medication reduction so far and this will need to be taken into account when considering its use in patients with a high medication burden.

Ab-interno canaloplasty: Safety profile

Safety appears to be favourable, and according to Heersink *et al.*^[12], inflammation was the most common adverse event in the combined group and occurred in 6% of participants, while loss of visual acuity was the most common adverse event in the control group, occurring in 8% of participants.

Trabectome: Mechanism of action and efficacy

Trabectome or ab-interno trabeculectomy achieves an increase in aqueous humor outflow through the trabecular meshwork by applying a 0.8 W electrical current in order to ablate the trabecular meshwork. Access to the anterior chamber is achieved through a clear corneal incision and gonioscopy is used intraoperatively to visualise the trabecular meshwork. Trabectome and ABiC are significantly differentiated from the other trabecular microbypass techniques, as no indwelling devices are left in the eye after the operation. Esfandiari *et al.*^[13] demonstrated the efficacy of Trabectome when compared against iStent implantation (both with phacoemulsification), and after 24 months a mean IOP of 13.9 ± 3.3 mmHg was achieved in Trabectome patients ($n = 154$) compared with 16.8 ± 2.8 mmHg in iStent ($n = 110$) from a baseline of 15.3 ± 3.1 mmHg in both groups. Medication burden was 0.7 ± 1.0 and 1.7 ± 1.2 in the trabectome and iStent groups, respectively, at 24 months. In addition, the proportion of eyes with an unmedicated IOP of ≤ 21 mmHg was 53% and 16.6% in the trabectome and iStent eyes, respectively^[13].

Trabectome has also demonstrated efficacy in pseudoexfoliative glaucoma. Avar *et al.*^[14] investigated Trabectome performed on patients either as a solo procedure or with concomitant cataract extraction (in combined data) described a significant IOP lowering effect in 28% of patients with POAG and 26% with pseudoexfoliative glaucoma, as well as a significant medication reduction in 32% and 29%, respectively. The median follow-up period in this study was 3.5 years^[14].

Gonioscopy assisted transluminal trabeculotomy

Gonioscopy assisted transluminal trabeculotomy (GATT) is a procedure where a circumferential trabeculotomy is performed of the trabecular meshwork, by running a suture the entire length of Schlemm's canal, retrieving and pulling the distal tip while applying traction to the proximal end of the suture. A study of XEN compared with GATT (both with or without cataract extraction, in combined data) showed that IOP was reduced from 24.9 ± 5.8 mmHg to 15.3 ± 3.8 mmHg at 24 months post-operatively, and medications were reduced from 3.3 ± 0.6 to 1.2 ± 0.4 . This is compared to a reduction in IOP from 24.4 ± 4.3 mmHg to 14.2 ± 2.2 mmHg at 24 months and medication reduction from 3.4 ± 0.5 to 2.0 ± 2.2 over the same period for the XEN gel stent. Transient hyphaema was the most common post-operative complication following GATT, occurring in 28% of patients^[15].

Excisional goniotomy

Excisional goniotomy or trabeculotomy facilitates increased aqueous outflow by utilising a device such as the Kahook Dual Blade (KDB, New World Medical, Rancho Cucamonga, CA) to incise the trabecular meshwork and in theory avoid the thermal damage associated with Trabectome or leaving remnant trabecular meshwork leaflets in-situ such as with GATT. In a 315-eye study comparing both iStent and Kahook Dual Blade in combination with phacoemulsification found that the mean IOP reduction at 12 months was 5.0 mmHg compared with 2.3 mmHg in the iStent group ($P < 0.001$) and mean medication reductions were similar in both groups with 1.03 and 0.97 in the Kahook Dual Blade group and the iStent group, respectively. Transient IOP elevation and transient anterior chamber inflammation were the most complications following KDB, both occurring in 1% of patients^[16].

MIGS aimed at creating an outflow channel to the supraciliary space

Mechanism of action, effectiveness, and safety profile.

CyPass: Mechanism of action and efficacy

CyPass (Transcend Medical Inc, Menlo Park, CA, USA) was a tubular stent which aimed to reduce IOP by shunting fluid through a passage into the supraciliary space. It was performed through a clear corneal incision, and the stent is placed inferior to the trabecular meshwork and advanced into the suprachoroidal space. CyPass had proven efficacy in the COMPASS trial which compared CyPass combined with phacoemulsification to phacoemulsification alone. It was shown that at 2 years, patients who had received the CyPass microstent had a mean reduction in IOP of 7.4 ± 4.4 mmHg (30%) compared to 5.4 ± 3.9 mmHg (21%) in the control group ($P < 0.001$ for CyPass microstent vs. control). A reduction from baseline values of 17.0 ± 3.4 mmHg and 19.3 ± 3.3 mmHg, respectively. This efficacy was also shown in the reduction in medications, as medications at 2 years had dropped from 1.4 ± 0.9 to 0.2 ± 0.6 in the CyPass group and from 1.3 ± 1.0 to 0.6 ± 0.8 in the control group. At 2 years 85% of CyPass recipients had maintained their IOP with no medications, compared to 59% in the phacoemulsification alone cohort^[17].

CyPass has also been compared with iStent in a head-to-head meta-analysis by Fard *et al.*^[19], and in that study, they showed that CyPass alone (without phacoemulsification) was a more effective intervention for reducing IOP than either 1 or ≥ 2 iStents with or without phacoemulsification, but both techniques were comparable in terms of medication reduction.

CyPass: Safety concerns

The COMPASS XT study was an extension of the original 24-month study for an additional 36 months to assess the safety of the stent. This study showed comparable safety between the study and control groups, and while there were 2 sight threatening complications in the CyPass group compared with only one in the control group, these were deemed to be unrelated to the stent. Despite this, evidence was found for increased corneal endothelial cell loss compared with the group that underwent phacoemulsification alone, and due to this it was announced in August 2018 that it would be voluntarily removed from the market by Alcon due to the potential risks, with the potential for reintroduction in the future^[18].

iStent Supra: Mechanism of action, effectiveness, and safety profile

iStent Supra (Glaukos Inc, Laguna Hills, CA, USA) is currently an experimental microbypass stent which also harnesses the uveoscleral pathway similarly to CyPass. Myers *et al.*^[20] evaluated iStent Supra in combination with 2 iStents and post-operative Travoprost for the treatment of refractory open angle glaucoma following trabeculectomy and maximal medical therapy. The pre-operative mean medicated IOP was 22.0 ± 3.1 mmHg, with 1.2 ± 0.4 medications on average. The post-operative mean medicated IOP at 48 months was ≤ 13.7 mmHg (12.9 ± 0.9 mmHg at month 48) and unmedicated mean IOP was 18.4 ± 1.4 mmHg at month 49 (post-washout). The safety profile of the suprachoroidal stent was favourable, and throughout the 48-month follow-up no patients required additional glaucoma surgery^[20].

Assessing the efficacy of iStent supra in this form of study alone is challenging, as there are confounding variables in the form of the 2 iStent devices, and the effects of the topical Travoprost. Further studies to determine the efficacy of iStent supra would be beneficial, preferably in the form of randomised controlled studies, and in comparison, with other methods or in combination with phacoemulsification.

MIGS targeted at the subconjunctival space

Mechanism of action, effectiveness, and safety profile.

Xen: Mechanism of action and effectiveness

The XEN gel implant (Allergan inc, Irvine, CA, USA) was a form of MIGS targeting aqueous outflow to the subconjunctival space; however, in November 2019, Allergan Australia Pty Ltd. announced that there would be a voluntary global recall of all un-implanted XEN units due to a portion of them failing quality control. They did not recommend the explantation of implants that had already been placed^[27].

The XEN gel stent was implanted into the trabecular meshwork with a needle through an ab-interno approach, which was then advanced to puncture the sclera entirely and pass the flexible stent into the subconjunctival space. This then creates a channel for aqueous humour outflow and creates an internal bleb to reduce IOP. XEN was indicated for moderate to advanced glaucoma, as it was a bleb-based procedure with the associated risks/complications associated with this. Karimi *et al.*^[22] investigated the efficacy of XEN alone or in combination with phacoemulsification with a 259 eye consecutive case series. The results showed that mean IOP (of both groups combined) was reduced from 19.3 ± 6.0 mmHg at baseline to 13.5 ± 3.3 mmHg at 18-month follow-up, and medications were reduced from 2.6 ± 1.1 to 1.1 ± 1.3 at 18 months. It was also interesting to note that simultaneous cataract extraction or solo stent implantation did not significantly impact outcomes, as these groups had an IOL of 13.8 ± 2.6 mmHg and 14.3 ± 4.7 mmHg at 12-month follow-up, respectively ($P = 0.5367$)^[22].

As a form of bleb forming procedure, it is also important to compare the XEN gel stent with trabeculectomy, which is still the predominant incisional procedure for glaucoma. Wagner *et al.*^[23] compared the 2 as standalone procedures performed in a 171-eye study, which demonstrated that complete surgical success at 12 months post-operative follow-up was higher in the trabeculectomy group at 65.5% (95%CI: 55.6%-75.9%) compared with the XEN gel stent group at 58.5% (95%CI: 47.6%-69.4%). There was however no significant difference between both groups' surgical outcomes ($P = 0.16$). In addition, an IOP reduction at 12-month follow-up of 7.2 ± 8.2 mmHg in the XEN group and 10.5 ± 9.2 mmHg in the trabeculectomy group were observed from baseline values of 19.0 mmHg (95%CI: 16.8-25.0 mmHg) and 21.0 mmHg (95%CI: 17.0-27.0 mmHg), respectively ($P = 0.003$). Medication reduction was also reduced to 0.3 ± 0.5 and 0.2 ± 0.4 in the XEN and trabeculectomy cohorts, respectively from baseline values of 2.0 (95%CI: 1.0-3.0) and 3.0 (95 CI: 2.0-4.0), respectively^[23].

The XEN gel stent was also shown to have comparable efficacy in other secondary forms of open angle glaucoma, including pseudo exfoliation glaucoma as demonstrated by Gillmann *et al.*^[24], where 110 eyes with either pseudoexfoliative OAG or POAG underwent either XEN as a standalone or with cataract surgery (with data combined). In this study the mean medicated IOP was 14.2 ± 3.8 mmHg (a 28.3% reduction) in the pseudoexfoliative group compared with 14.5 ± 3.6 mmHg (a 26.8% reduction) in the POAG group after 2 years, a reduction from 19.8 ± 8.2 mmHg and 19.8 ± 5.8 mmHg respectively. Medication reduction was also comparable, with a drop from 2.0 ± 1.3 to 0.4 ± 0.7 in pseudoexfoliation glaucoma and from 1.9 ± 1.6 to 0.6 ± 0.9 in POAG. Success rates were not different to a statistically significant degree, and the rate of adverse effects and rates of needling were similar in both groups (42.8% POAG vs. 43.2% pseudoexfoliative)^[24]. There were no studies showing evidence of the efficacy of the XEN implant in pigmentary or steroid induced glaucoma.

Xen: Safety profile

Important to note is that 40.9% of cases required post-operative management including bleb needling or the administration of an antimetabolite injection, and adverse events included IOP spikes of ≥ 30 mmHg (12.7%), follow-up glaucoma filtration surgery (9.3%), exposure of the implant (2.3%) as well as some cases of persistent hypotonous maculopathy, persistent choroidal effusions, a cyclodialysis cleft and endophthalmitis following bleb resuturing^[22]. This is partially to be expected with a bleb forming operation and reflects the safety profile of this class of procedure.

Preserflo microshunt: Mechanism of action, effectiveness, and safety profile

The Preserflo microshunt (Santen Inc, Emeryville, CA, USA) previously known as the InnFocus microshunt aims to address the need for a form of MIGS that can be effectively applied to moderate to severe glaucoma. The Preserflo device is implanted into the subconjunctival space below Tenon's capsule via an ab-externo approach and threaded through a needle tunnel into the anterior chamber. The biocompatible material of the Preserflo tube (SIBS) in combination with intraoperative Mitomycin C is used to reduce the risk of scarring and fibrosis. Sadruddin *et al.*^[25] showed in a 23 patient post-market study of Preserflo with and without phacoemulsification, a reduction from the mean baseline IOP in both groups of 23.8 ± 5.3 mmHg (26.4 mmHg in phacoemulsification combination group vs. 22.1 mmHg for Preserflo alone) to 10.7 ± 3.5 mmHg at 3-years follow-up (10.2 mmHg with phacoemulsification vs. 11.1 mmHg for Preserflo alone). Medication reduction was 71% overall at 3 years, and 64% of participants no longer required topical glaucoma medications^[25].

Transient hypotony, shallow anterior chambers and the device touching the iris occurred in 13% of patients individually, while transient choroidal detachment, hyphema and exposed Tenon's capsule were also common adverse events occurring in 9% of patients respectively. All of these issues resolved spontaneously within 3 months of surgery being performed^[25].

There is currently a lack of randomised control trials on the efficacy of Preserflo, however one RCT is in progress and with more high-level evidence the safety and efficacy of this novel method will be made increasingly clear in order to establish it as a viable option in OAG management.

MIGS targeting the ciliary process

Endocyclophotocoagulation: Mechanism of action, effectiveness and safety profile

Endocyclophotocoagulation (ECP) is a procedure that can be performed in conjunction with phacoemulsification for refractory glaucoma and aims to reduce the production of aqueous humor by the ciliary processes by shrinking these using a directed laser. ECP is generally indicated in end-stage glaucoma. Pantalon *et al.*^[21] have demonstrated the efficacy of ECP through conducting a 12-month retrospective study with patients receiving either 2 iStents, with concurrent ECP and cataract extraction, or phacoemulsification and 2 iStents alone. The ECP procedure proved efficacious in reducing IOP from a baseline value of 19.97 ± 4.31 mmHg to 13.05 ± 2.18 mmHg (a 35% reduction) compared with 17.63 ± 3.86 mmHg to 14.09 ± 1.86 mmHg (a 21% reduction) in the phacoemulsification and 2 iStent alone group. Medications were also reduced from 2.22 ± 1.6 to 1.24 ± 1.05 in the ECP group and from 2.07 ± 1.02 to 1.39 ± 1.03 in the phaco-iStent alone group, a comparable reduction in both, and safety results were also comparable. These results appear promising for the utilisation of ECP as a combined procedure with other MIGS and cataract surgery^[21].

There is, however, limited knowledge of the safety profile of ECP due to the lack of high-level evidence in the form of randomised controlled trials. One study, currently in the data collection phase, is investigating patients with POAG receiving either ECP with phacoemulsification or phacoemulsification as a standalone procedure^[28].

Emerging MIGS procedures

MINIject

The MINIject device (iStar Medical, Wavre, Belgium) is a 4 mm stent designed to follow the curvature of the sclera and utilises porous silicone to allow aqueous outflow via the uveoscleral pathway. No studies were identified investigating the MINIject device, and this is an area where more evidence is required before a clear comment can be made about this form of MIGS^[29].

Beacon aqueous microshunt

This device is designed to reduce IOP by shunting aqueous fluid onto the ocular surface via a clear corneal incision. There are currently no clinical trials on this device^[29].

CONCLUSION

Minimally invasive glaucoma surgery has, for several years, been a disrupting force in the area of glaucoma management and is a therapy that has effectively established itself between medical management and more invasive glaucoma surgery. MIGS offer significant advantages in terms of safety and efficacy for the patient with mild to moderate glaucoma and a significant medication burden. As this area of glaucoma surgery continues to grow, so too will the evidence in support of MIGS as a legitimate intermediate step in the glaucoma management pathway.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Komzak K, Rothschild P, Hooshmand J, Allen P, Toh T

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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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Robotic Ivor Lewis esophagectomy

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Abstract

The addition of robotic-assistance is the latest evolution of minimally invasive esophageal resection and reconstruction. Despite the improved visualization, the addition of wristed instrumentation, and improved ergonomics, there remains a significant learning curve for complex procedures like esophagectomy. In experienced, high-volume centers, robotic-assisted minimally invasive esophagectomy (RAMIE) has demonstrated outcomes equivalent to traditional laparoscopic and thoracoscopic minimally invasive esophagectomy. Herein, the RAMIE procedure is described in detail in key steps. This approach has been established as safe and effective for esophagectomy.

Keywords: Robotic esophagectomy, esophagectomy, esophageal cancer, Ivor Lewis, robotic-assisted minimally invasive esophagectomy

INTRODUCTION

Worldwide, esophageal cancer is the seventh most commonly occurring cancer in men and the 13th most commonly occurring cancer in women^[1]. Overall, there are 572,000 new cases per year and esophageal cancer carries the sixth-highest overall mortality, being responsible for an estimated 1 in every 20 cancer deaths in 2018^[1]. Although also performed for benign diseases, esophageal cancer represents the most common indication for esophagectomy^[2]. In this work, we outline the general principles of the preoperative evaluation, technical details of intraoperative steps, and the outcomes of robotic-assisted minimally invasive esophagectomy (RAMIE).



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BACKGROUND

As a complex, multi-cavity procedure, Ivor Lewis esophagectomy requires a thorough understanding of surgical anatomy, technical skill, and perioperative care to achieve acceptable outcomes. The first successful transthoracic esophagectomy was performed in 1913 by Dr. Torek^[3], which marked the beginning of the open surgical era that was plagued by high morbidity. Even in this modern era, outcomes can vary widely, with mortality ranging from 8%-23%, largely dependent upon hospital volume^[4]. However, in experienced centers, an acceptable 30-day (and even 90-day) hospital and/or overall mortality below 5% is often achieved and becoming the standard^[5]. The initial descriptions of a minimally invasive esophagectomy (MIE) in the early 1990s by Drs. Cuschieri *et al.*^[6], Dallemagne *et al.*^[7], and DePaula *et al.*^[8] ushered in a new era of esophageal surgery. The safety, feasibility, oncologic soundness, and reproducibility of MIE were validated in Eastern Cooperative Oncology Group (ECOG) 2202, a large, multicenter, prospective, randomized trial published in 2015^[9]. As the MIE was gaining popularity, the first report of a RAMIE was published by Dr. Horgan *et al.*^[10] in 2003. Since its introduction, RAMIE has been validated against the standard open and minimally invasive approaches^[11]. When compared to open esophagectomy, RAMIE has demonstrated intraoperative benefits including less blood loss and more complete lymphadenectomy, despite its longer operative time. RAMIE showed faster convalescence with a shorter length of stay (LOS), decreased pain, decreased intensive care unit (ICU) admissions, and fewer infectious and cardiopulmonary complications. There were no consistent differences in overall major complications, anastomotic leak rate, and 90-day mortality^[11-13]. When directly compared to MIE, RAMIE resulted in longer operative time, but no significant difference in blood loss, overall complication rate, length of stay, or the number of total dissected lymph nodes^[14].

PREOPERATIVE PREPARATION

Risk stratification

In efforts to define and reduce significant morbidity and mortality, multiple attempts have been made to define the risk factors associated with the adverse outcomes of esophagectomy. A large, prospective analysis of the Department of Veterans Affairs (VA) National Surgical Quality Improvement Program (NSQIP) database identified both preoperative and intraoperative risk factors for morbidity and mortality. Preoperative predictors impacting mortality included neoadjuvant therapy, decreased functional status, increasing age, insulin-dependent diabetes mellitus, and signs of hepatic dysfunction (elevated blood urea nitrogen, elevated alkaline phosphatase, alcohol abuse, and ascites), while the addition of dyspnea with mild exertion, chronic obstructive pulmonary disease, decreased serum albumin concentration, and an increased complexity score increased overall morbidity^[15]. Intraoperative risk factors for morbidity included the need for blood transfusion and prolonged operative time, while only transfusion requirement impacted mortality^[15]. A review of the Society of Thoracic Surgeons General Thoracic Surgery Database revealed age > 65, BMI \geq 35, preoperative congestive heart failure, Zubrod score > 1, McKeown Esophagectomy, current or former smoking status, and squamous cell histology to be significant predictors of combined major morbidity or mortality^[16].

A preoperative esophagectomy risk score, developed as a composite of the revised cardiac risk index, the model for end-stage liver disease score, and the pulmonary function test, was found to be an independent predictor of tumor recurrence and overall survival^[17]. At our institution, we routinely calculate the Risk Analysis Index (RAI), which is a practical, prospective frailty assessment tool requiring only a median of 33 s to complete and demonstrates a dose-dependent relationship with mortality, overall LOS, ICU LOS, and readmission. When comparing patients using an RAI cutoff of \geq 37 with those < 37, there was a 60% higher 30-day and 90-day readmission rate, twice the rate of an extended LOS > 14 days, and almost twice the rates of prolonged ICU stay. When comparing for 180-day mortality, an RAI of < 37 carried an NPV of 98.6%

while an RAI of ≥ 37 had a PPV of 10.7%^[18].

Disease specific

In addition to the aforementioned assessments, additional testing is performed selectively based on the patient's underlying ailment.

Malignancy

Once malignancy is confirmed by endoscopic biopsy, staging is completed with endoscopic ultrasound (EUS), computed tomography (CT) with fluorodeoxyglucose-18 positron emission tomography (PET), and/or staging laparoscopy with gastric extension^[19]. Upfront surgery is offered for selected patients with node-negative clinical T1a or T1b tumors, and patients with T2 N0 disease. For patients with potentially resectable disease that are clinically node-positive or at high-risk for node positivity (cT3-4), neoadjuvant chemotherapy with or without radiation is performed before restaging and consideration for surgery. Patients with local-regional disease unfit for surgery are treated with definitive chemoradiotherapy. This approach echoes with that outlined by the American Society of Clinical Oncology in their recent guideline^[20].

Benign

Less commonly performed for benign indications than for malignant, esophagectomy remains a definitive treatment for several conditions. End-stage achalasia, previously failed (often multiple) operations for gastroesophageal reflux disease (GERD) and/or hiatal hernia, and trauma account for 84% of esophagectomies for benign indications^[21]. Other less common indications in selected patients include motility disorders (diffuse esophageal spasm, scleroderma), strictures, benign tumors, spontaneous or iatrogenic perforations, congenital anomalies, and caustic ingestion.

The preoperative workup is tailored to the exact benign indication. At a minimum, esophagoscopy and fluoroscopic esophagram are required. Frequent additions include but are not limited to CT scans, esophageal manometry, esophageal pH monitoring, endoscopic ultrasound, endobronchial ultrasound, gastric emptying studies, and bronchoscopy.

OPERATIVE TECHNIQUE

Despite many technological advances, the principles and techniques of minimally invasive esophagectomy at the University of Pittsburgh remain largely unchanged from Dr. Luketich's early description in the 1990s^[2,22-24]. Especially for those with prior minimally invasive esophageal surgery experience, the robotic techniques described are largely an evolution of the traditional minimally invasive concepts rather than a unique procedure, albeit with far more sophisticated instrumentation^[25]. Here, we describe in detail the Ivor Lewis esophagectomy for malignant diseases and also discuss minor differences in procedures for benign indications.

Pre-incision

Although often overlooked, the period prior to an incision should be used as an opportunity to maximize the chances of a successful surgery. The team should review the case specifics ahead of time and outline a clear plan for the conduct of the operation. Attention should be paid to emergency contingencies and plans for such events should be verbalized.

Anesthesia

The patient should be anesthetized under general anesthesia with a double-lumen endotracheal tube, adequate IV access, and invasive hemodynamic monitoring. If a central venous catheter is inserted, we prefer to avoid the left neck and chest in the event a cervical esophagostomy is required. The position of the double lumen endotracheal tube is confirmed with fiberoptic bronchoscopy. Alternatively, newer double lumen endobronchial blockers may be utilized through a single lumen endotracheal tube (Rusch EZ-Blocker, Teleflex). All patients receive venous thromboembolism prophylaxis with sequential compression devices and subcutaneous heparin. Perioperative antibiotics should comply with Surgical Care Improvement Project measures, with cefazolin being the first-line of choice^[26]. Communication between the surgeon and anesthesia provider is crucial to the conduct of the operation. The surgeon should be made aware of the patient's hemodynamic changes at all times. Once the gastric vasculature is divided, hypotension should generally be treated with volume expansion as opposed to vasopressors to minimize conduit ischemia.

Endoscopy

Flexible fiberoptic esophagogastroscope is routinely performed at our institution. This allows for a final assessment of the esophageal pathology for which the esophagectomy is indicated. The stomach and esophagus should be decompressed on withdrawal of the scope to allow for safe laparoscopic port placement and subsequent visualization.

Laparoscopy

Ivor Lewis esophagectomy begins in the abdomen and progresses through an assessment for metastatic disease, esophagogastric mobilization with lymphadenectomy, conduit creation, pyloroplasty, and feeding jejunostomy insertion.

Positioning

The patient is placed in a supine position on the operating table with a footboard to allow for safe steep reverse-Trendelenburg positioning. The left arm is tucked and the right arm is extended to approximately 45 degrees. For non-robotic procedures, the surgeon stands on the patient's right side with the assistant standing on the left. A liver retractor (Lapro-Flex® Triangular Retractor, Mediflex, Islandia, NY) is attached to the right side of the bed between the knee and hip.

Port placement

Abdominal port placement is shown in [Figure 1](#). Although we find these locations to be the most useful, port placement may vary based on surgeon preference or patient factors. The peritoneal cavity is accessed per surgeon comfort, although we prefer starting with an optical separator 5 mm robotic port in the left midclavicular line approximately 3 cm inferior to the costal margin. This port will be replaced with an 8 mm robotic port and used for the robotic right arm (arm 3). In a potentially hostile abdomen, the location and method of entry should be tailored to the scenario with a focus on safety. The abdomen is insufflated, and a 30-degree camera is introduced into the abdomen. Adhesiolysis is performed as necessary to facilitate placement of subsequent ports under direct laparoscopic visualization. Three additional robotic working ports, a port for the liver retractor, and two bedside assistant ports are placed. The additional robotic ports include a 12 mm robotic port with an 8 mm reducing sheath in the right midclavicular line approximately one-third from the umbilicus to xiphoid for the robotic left arm and stapler (arm 1), an 8 mm robotic port just to the left of midline approximately one-third from the umbilicus to xiphoid for the camera (arm 2), and an 8 mm robotic port in the left anterior axillary line 2-3 cm inferior to the costal margin for the robotic assist (arm 4). The laparoscopic liver retractor port is placed inferior to the costal margin in the right midaxillary line just anterior to the peritoneal reflection of the hepatic flexure of the colon. The bedside

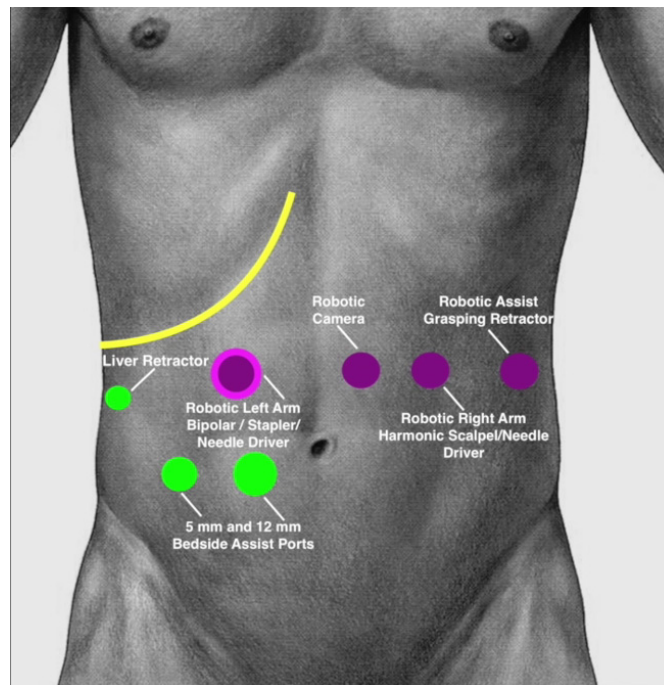


Figure 1. Port location for abdominal portion. The yellow line denotes the costal margin. This figure is quoted with permission from Ekeke *et al.*^[27].

assistant ports are placed in the right lower paraumbilical region and include an 11 mm laparoscopic port just medial to the midclavicular line and a 5 mm laparoscopic port approximately a hands breadth lateral to the 11 mm port. The patient is placed in a steep reverse-Trendelenburg position to displace the viscera from the diaphragm. The liver retractor is inserted, and the left lobe of the liver is elevated.

Docking

The da Vinci Xi robotic side cart (Intuitive Surgical, Sunnyvale, CA) is brought in from the patient's right at the level of the torso and the camera port is docked to arm 2. The hiatus is targeted, the remaining arms are docked, the instruments are inserted, and patient clearance is optimized. A da Vinci Force Bipolar grasper (Intuitive Surgical, Sunnyvale, CA) is initially inserted into arm 1 (robotic left hand), an ultrasonic shear is inserted into arm 3 (robotic right hand), and a da Vinci small grasping retractor (Intuitive Surgical, Sunnyvale, CA) is inserted into arm 4 (robotic assist). The bedside assistant utilizes a suction and a laparoscopic grasper.

Crural assessment

Dissection begins by excising the gastrohepatic ligament to expose the caudate lobe of the liver and the right diaphragmatic crus. The dissection should stay close to the liver from the porta hepatis to the right crus to reflect any lymphoid tissue with the specimen. A replaced or accessory left hepatic artery is occasionally encountered in the gastrohepatic ligament. Preservation of this artery makes the remaining operation more difficult but should be considered if the vessel appears to represent a significant contribution to hepatic circulation, such as a replaced left hepatic artery. If there is doubt, the vessel can be temporarily occluded, and the liver can be observed for signs of ischemia before division. The phrenoesophageal ligament is incised circumferentially and the esophagus is mobilized from the crura. If there is diaphragmatic invasion by the tumor, the muscle may be resected en bloc with the specimen. The mobilization continues anteriorly along the pericardium and posteriorly along the aorta to assess for tumor invasion that may render the

tumor unresectable [Figure 2].

Retrogastric dissection

To expose the left gastric vascular pedicle, the stomach is retracted anteriorly by passing the robotic assist arm posterior to the stomach, medial to the left gastric pedicle, and into the lesser sac with the bedside assistant elevating the gastroesophageal junction [Figure 3]. The origin of the left gastric artery and vein are identified, and the lymphatic tissue is reflected with the specimen [Figure 4]. The lymphadenectomy continues along the splenic and common hepatic vascular pedicles to complete the celiac dissection. The left gastric artery and vein are divided with a robotic vascular staple load [Figure 5]. Initial short gastric dissection is initiated from a retrogastric approach and continues along the gastrosplenic hilum [Figure 6].

Greater curvature dissection

The robotic assist arm and bedside assist arm are advanced posterior to the stomach towards the left upper quadrant to expose the short gastric vessels in the retrogastric plane. Greater curve dissection, along with completion of the gastrosplenic ligament dissection initiated from the retrogastric approach, is continued along the fundus from proximal to distal while individually ligating the short gastric vessels with ultrasonic shears. Especially in patients with preoperative radiotherapy, a pedicled omental flap can be created along two sequential omental branches off the gastroepiploic arcade during this portion of the mobilization (not shown). The retrogastric attachments to the retroperitoneum are divided. The dissection continues along the greater curve of the stomach to approximately the pylorus. The lesser curve of the stomach is then gently grasped with arm 4 in an area that will be included with the specimen and is retracted towards the hiatus/liver. Taking care to avoid injuring the gastroepiploic vascular arcade, the dissection continues along the greater curve of the stomach and omentum, completely freeing the attachments that restrict mobilization of the stomach. A partial or complete Kocher maneuver may be completed if desired by the surgeon. The remaining retroantral attachments are divided. Adequate tension-free mobilization is confirmed by ensuring that the pylorus reaches the right crus of the diaphragm.

Conduit creation

The pylorus is identified and a site on the stomach approximately 5-6 cm proximal to the pylorus is identified as the distal aspect of the gastric tube. The stomach is oriented for conduit creation with the arm 4 robot assist retracting the fundus towards the apex of the left hemidiaphragm, thus clearly delineating the orientation and lay of the future conduit [Figure 7]. Once the conduit is initiated, the robotic right-hand arm 3 “hooks” and retract the neo-lesser curve inferiorly to provide traction and better reveal the anticipated staple path to create a linear conduit. The first robotic stapler firing is a vascular load and traverses and ligates the lesser curve vasculature [Figure 8]. A 3 cm gastric conduit is then created with multiple fires of the robotic stapler parallel to the greater curve of the stomach [Figure 9]. Care should be taken to keep the staple line parallel to the short gastric line for proper orientation. The proximal tip of the conduit should be divided at a point that allows for adequate conduit length but maintains an appropriate oncologic margin. The tip of the conduit is tacked to the specimen in anatomic orientation with a horizontal mattress suture and the omental flap (if created) is tacked to the tip of the conduit. A marking stitch is placed on the conduit staple line at the junction between the future subdiaphragmatic antral reservoir and the supradiaphragmatic neo-esophagus. The specimen and proximal conduit may be tucked into the mediastinum. A cruroplasty is not routinely performed unless the hiatus is exceptionally enlarged.

Pyloroplasty

The role of pyloroplasty is debated but is frequently performed. When performed, a Heineke-Mikulicz pyloroplasty is utilized. The pylorus is identified, using endoscopy if necessary. Stay sutures are placed at the

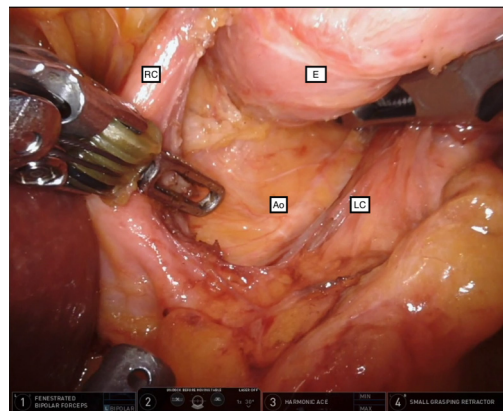


Figure 2. Early circumferential hiatal mobilization is performed to assess the extent of local disease and ensure resectability. E: Esophagus; RC: right crural pillar; LC: left crural pillar; Ao: aorta.

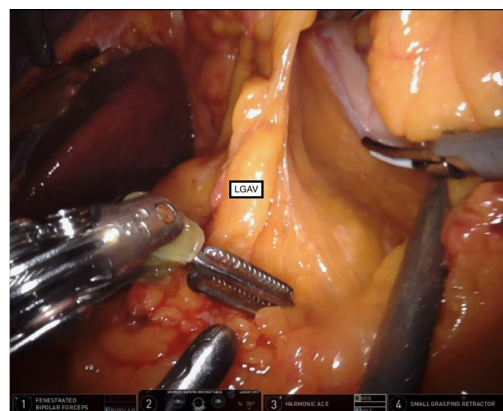


Figure 3. Retrogastric exposure is obtained by retracting the stomach anteriorly by passing the robotic assist arm into the lesser sac and elevating the gastroesophageal junction anteriorly. The bedside assist arm provides further retraction of the stomach and lesser omentum, as shown, to clearly expose the vascular pedicle and retrogastric space. LGAV: Left gastric artery and vein.

lateral aspects of the pylorus including the vein of Mayo. The robotic left arm grasps the “superior” stay suture (screen orientation) and the bedside assistant grasps the “inferior” stay suture to apply traction on the pylorus. The pylorus is divided along its full width with a longitudinal full-thickness antro-duodenal incision [Figure 10]. The lumen should be inspected to ensure no injury to the back wall and complete division of the muscle. The defect is closed transversely with 2-0 non-absorbable braided sutures [Figure 11]. The sutures must be of full-thickness to include the mucosa, but avoid catching the back wall. A portion of the omentum can be secured over the closure for added protection from a leak.

Feeding jejunostomy

Traditionally, feeding jejunostomy tubes are placed at the time of esophagectomy for nutritional support. While we advocate routine placement of a feeding tube, like pyloroplasty, there is some debate and equipoise regarding the necessity of this procedure^[28]. Although it can be performed with robotic assistance, we elect to perform this with routine laparoscopy as the last part of the abdominal procedure. The robotic instruments are removed and the robot is undocked from the patient. With a 5 mm 30-degree laparoscopic camera in the 5 mm right lower quadrant port, and in-line graspers in the right subcostal robotic port and the right lower quadrant 12 mm port, the transverse colon is retracted cranially to expose the ligament of Treitz. The jejunum is measured for a length of 35-40 cm, and a loop near this distance is selected that easily

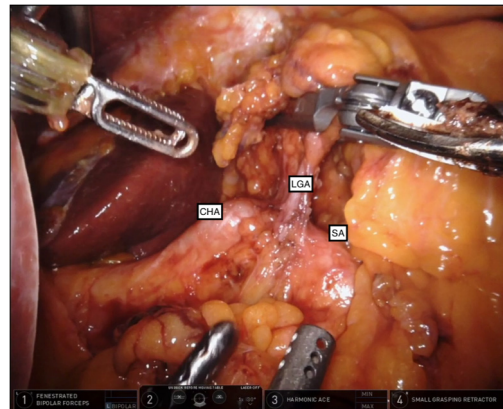


Figure 4. The celiac axis is skeletonized along the left gastric vascular pedicle, splenic artery, and common hepatic artery. All lymph node bearing tissue is dissected, elevated, and kept with the specimen. LGA: Left gastric artery and vein; CHA: common hepatic artery; SA: splenic artery.

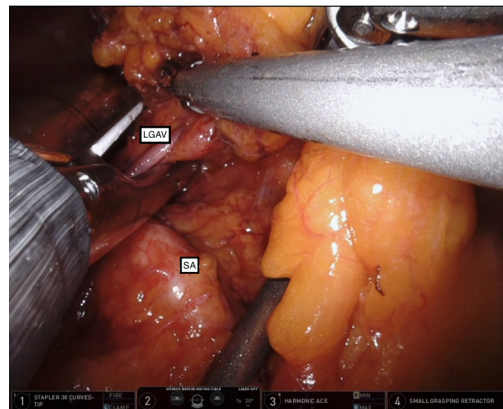


Figure 5. The left gastric artery and vein are divided with a robotic vascular stapler load. LGAV: Left gastric artery and vein; SA: splenic artery.

reaches the anterior abdominal wall. An insertion site in the left lower quadrant is selected and a 25-gauge needle is inserted through the skin to identify the jejunostomy tube site. The jejunum is then sutured to the abdominal wall with a 2-0 Surgidac Endostitch (Medtronic, New Haven, CT), keeping the orientation of the afferent and efferent limbs. The finder needle is exchanged for a Yueh needle, which is advanced through the abdominal wall into the jejunal lumen. The intraluminal position is confirmed by an air bolus. Next, a guidewire is inserted into the distal limb of the jejunum and the Yueh needle is removed. A skin incision is made, the dilator and sheath are advanced over the wire into the jejunal lumen under direct visualization, and the guidewire and dilator are removed leaving the sheath in place. A 10-French jejunostomy tube is trimmed to a length of 20 cm from the balloon, which is cut to avoid accidental inflation. The feeding tube is advanced through the sheath into the distal limb of jejunum and the sheath is removed. Two Witzel-type 2-0 Surgidac Endostitches are placed on the efferent jejunum and the jejunum is circumferentially sutured to the abdominal wall with a 2-0 Surgidac Endostitch. An additional 2-0 Surgidac Endostitch is placed a few centimeters distally as an anti-torsion stitch. The tube position is again confirmed by an air bolus. The feeding tube is secured to the bumper with a 2-0 silk suture and the bumper is secured to the skin with 2-0 silk sutures.

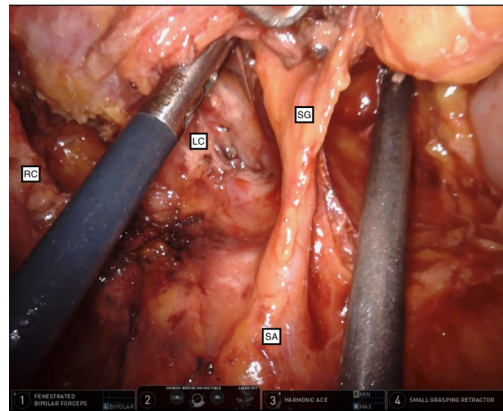


Figure 6. Greater curve dissection with individual ligation of the short gastric vessels is performed with the retrogastric approach. SG: Short gastric vessels; RC: right crural pillar; LC: left crural pillar; SA: splenic artery.

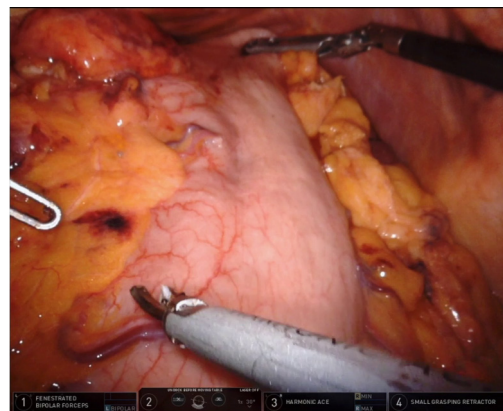


Figure 7. The stomach is oriented for conduit creation by retracting the tip of the fundus towards the apex of the left hemidiaphragm with the robotic assist (arm 4).

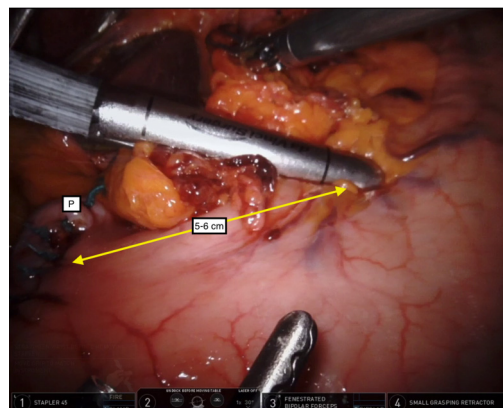


Figure 8. The first robotic vascular stapler is fired 5-6 cm proximal to the pylorus to include the lesser omentum and ending just on the stomach. P: Pylorus.

Closing

The liver retractor and its port are removed under direct visualization and the fascia of the port sites are

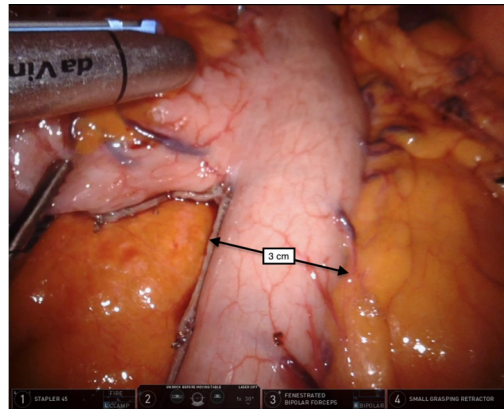


Figure 9. A 3 cm gastric conduit is created with multiple fires of the robotic endo-gastrointestinal stapler parallel to the greater curve of the stomach, and the insertion line of the left gastroepiploic and short gastric vessels. Note the clear orientation of the conduit-in-formation at all times.

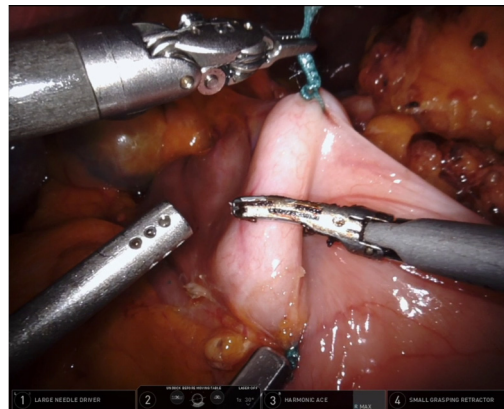


Figure 10. Pyloromyotomy is performed by dividing the pylorus longitudinally along its entire length with the ultrasonic scalpel. Note the “12 o’clock” and “6 o’clock” orientation of the pylorus created by traction on the lateral stay sutures.

closed according to surgeon comfort. We prefer to use a Carter-Thomason suture passer for entry sites 12 mm or greater (the right upper abdominal stapler port). Drains are not routinely placed in the abdomen. We frequently place a left pleural pigtail catheter after the abdominal portion of the operation before positioning the patient laterally. This allows for the evacuation of potential pneumothorax or pleural effusion if the left pleura is violated during the thoracic portion of the esophagectomy.

Thoracoscopy

After completion of the abdominal portion, Ivor Lewis esophagectomy proceeds in the chest for esophageal mobilization with en bloc mediastinal lymphadenectomy, specimen removal, and restoration of intestinal continuity by esophagogastrostomy.

Positioning

The patient is turned into the left lateral decubitus position on a padded beanbag. The bed is flexed to widen the intercostal spaces and the beanbag is deflated to secure the patient. A gel axillary roll is placed in the left axilla and the right arm is secured with an arm holder. The position of the double-lumen endotracheal tube is confirmed by bronchoscopy and the right lung is isolated.

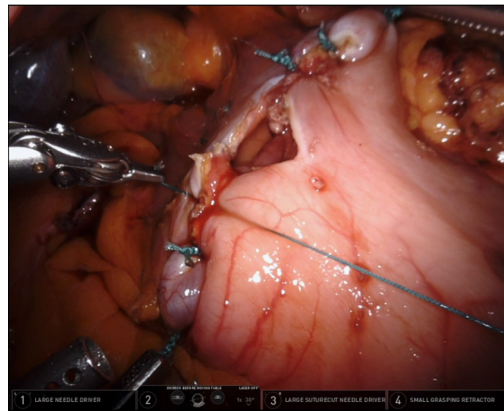


Figure 11. A Heineke-Mikulicz pyloroplasty is performed by closing the defect transversely. Sutures are alternated between the “upper” and “lower” lateral aspects of the defect to ensure an even closure.

Port placement

Thoracic port placement is shown in [Figure 12](#). Although rarely utilized, a standard thoracotomy incision is marked on the patient if emergent conversion to open is required [\[Figure 12\]](#). We prefer to enter the chest with an 8 mm robotic optical separator in approximately the 3rd or 4th intercostal space in the posterior axillary line (arm 4). Pneumothorax is established with CO₂ insufflation and additional ports are placed in this line in approximately the 8th or 9th space above the diaphragmatic insertion (arm 2) and approximately the 5th or 6th intercostal space (arm 3). An additional 8 mm port (arm 1) is placed at the “dome” or apex of the right lateral chest approximately “over” the right crural pillar in approximately the 9th or 10th intercostal space. The bedside assistant/robotic stapling port is a 12 mm robotic port with a 5-8 mm cap and is inserted halfway between the inferior two robotic ports at the insertion of the diaphragm.

Docking

The da Vinci Xi robotic side cart is brought in from the patient’s right at the level of the shoulders and the camera port is docked to arm 2. The azygous vein is targeted, the remaining arms are docked, the instruments are inserted, and patient clearance is optimized. A Force Bipolar Grasper is initially inserted into arm 1 (robotic left hand), an ultrasonic shear is inserted into arm 3 (robotic right hand), and a small grasping retractor is inserted into arm 4 (robotic assist). The bedside assistant utilizes a suction device.

Subcarinal dissection

The right lower lobe posterior basilar edge is retracted superiorly with the robotic assist arm and the inferior pulmonary ligament is divided to expose the inferior pulmonary vein. An intracorporeal rolled gauze “cigar” is inserted in the chest and is grasped by the robotic assist arm for anterior lung retraction. The pleura over the posterior hilum is incised along the pericardium to expose the bronchus intermedius. Dissection along the inferior edge of the airway continues to the carina, onto the posterior aspect of the trachea, and again distal onto the left mainstem bronchus. This sequence ensures clear and confident exposure of the left mainstem bronchus (the most common site of injury to the airway) and subsequent safe exenteration of all nodal tissue from the bronchi, left pleura, and pericardium [\[Figure 13\]](#). Care must be taken to avoid thermal injury to the posterior membranous airway, especially during minimally invasive esophageal resections^[29].

Posterior dissection

The pleura overlying the posterior esophagus is incised starting at the inferior edge of the azygous vein and

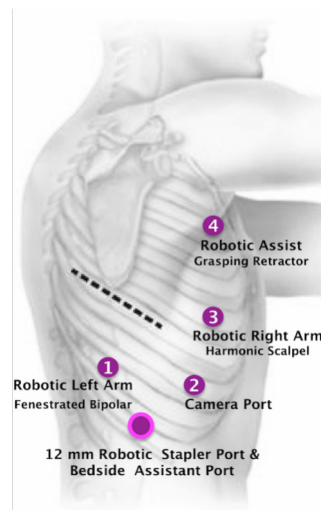


Figure 12. Port location for the thorax. The dashed line represents the standard thoracotomy incision. This figure is quoted with permission from Ekeke *et al.* [27].

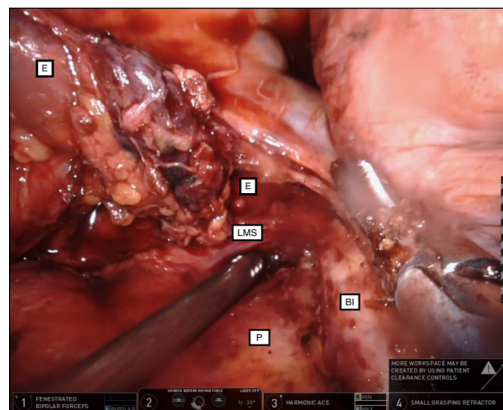


Figure 13. The subcarinal lymphadenectomy includes all nodal tissue between the bronchi, left pleura, and pericardium. Note the dissected lymph node packet swept up with the esophagus. LMS: Left mainstem bronchus; BI: bronchus intermedius; P: pericardium; E: esophagus.

extending to the hiatus. The pleura overlying the right diaphragmatic crural pillar is incised to meet the prior dissection along the pericardium, and the low paraesophageal lymph nodes along the diaphragm are reflected with the specimen. The pleura overlying the esophagus is grasped with the robotic assist arm and the esophagus is reflected anteriorly. The posterior esophagus is mobilized along the spine and aorta from the hiatus to the azygous with the bedside assistant placing clips on any tissue potentially containing branches of the thoracic duct, or the duct itself [Figure 14]. The pleura overlying the azygous vein is incised, and the vein divided with a robotic vascular staple load.

Proximal esophageal dissection

Above the level of the azygous vein, the dissection shifts to “hug” the esophagus [Figure 15]. The right vagus nerve is divided at the level of the azygous to avoid traction injury to the recurrent laryngeal nerve during the remaining dissection. The esophagus is circumferentially mobilized to the level of the thoracic inlet (if needed) to provide adequate mobility for the esophagogastric anastomosis.

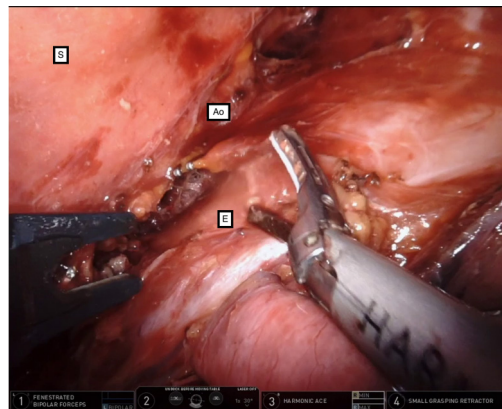


Figure 14. The posterior esophagus is mobilized along the spine while clipping any tissue potentially containing the thoracic duct or one of its branches. The robot assist (arm 4) can provide medial retraction on the esophagus away from the aorta. S: Spine; Ao: aorta; E: esophagus.

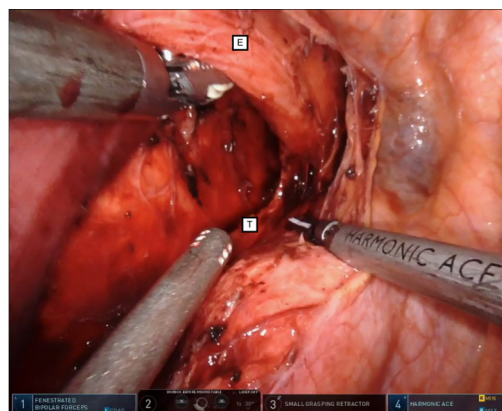


Figure 15. Circumferential dissection proximal to the azygous vein “hugs” the esophagus. E: Esophagus; T: trachea.

Completion of esophageal dissection

With the robotic assist (arm 4) elevating the esophagus, the esophagus is mobilized from the left pleura along its length to complete the circumferential esophageal mobilization with en bloc lymphadenectomy. The esophagus is divided with either a scissor or ultrasonic shears at a level appropriate for a sound oncologic margin. This may be as high as the thoracic inlet, but generally 2-3 cm proximal to the azygous vein for lower esophageal tumors [Figure 16]. The proximal stomach and the gastric conduit are pulled into the chest and the tacking suture is removed. The proximal conduit is temporarily sutured to the diaphragm to prevent retraction back into the abdomen.

Specimen removal and conduit preparation

The posterior robotic arm 1 is undocked and the port is removed. The incision is extended to approximately 4 cm and a small wound protector is inserted. Alternatively, a specimen retrieval bag can be inserted through the 12 mm bedside assist port, and the incision upsized on retrieval. The specimen is sent for frozen pathologic analysis of margins, which should be confirmed as benign prior to reconstruction.

Anastomosis

We utilize an extra-long circular end-to-end anastomotic (EEA) 28 mm stapler (DST XL 28mm EEA,

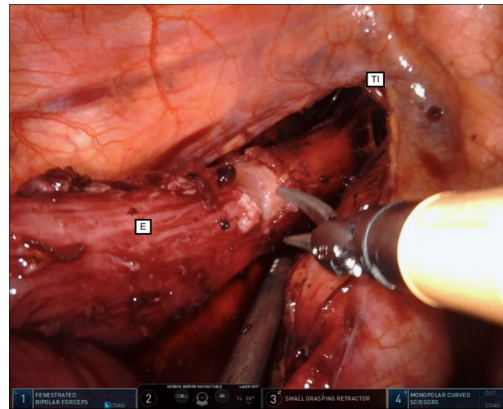


Figure 16. The esophagus is divided at a level appropriate for a sound oncologic margin, but no lower than the level of the azygous vein. Shown is division high in the chest at approximately the level of the thoracic inlet. E: Esophagus; TI: thoracic inlet.

Covidien, USA) to create an end-to-side (functional end-to-end) esophagogastrostomy. Regardless of the technique, the goal is to create a well-perfused, tension-free, properly oriented, pneumostatic, full-thickness anastomosis. The conduit needs to be of adequate length to avoid anastomotic tension, yet short enough to lay straight without redundancy. The redundant tip of the conduit is frequently ischemic or damaged from manipulation and is resected. The anastomotic site should be chosen at a location of healthy appearing conduit either by gross visualization or with the aid of indocyanine green near-infrared fluorescence imaging available on the robotic platform (Firefly, Intuitive Surgical, Sunnyvale, CA)^[30]. It is generally feasible to create the anastomosis just proximal to the site of the gastroepiploic vascular arcade termination.

To create an EEA stapled anastomosis, the stapler anvil is inserted into the chest through the anterior aspect of the access incision. The Force Bipolar is placed in the robotic left arm 1 and a large self-cutting needle driver (Large Suture Cut Needle Driver, Intuitive Surgical, Sunnyvale, CA) is placed in the robotic right arm 3. A running baseball stitch with 2-0 non-absorbable monofilament suture is placed. Care should be taken to ensure that each suture bite is full-thickness containing the mucosa, but not excessively deep (2-3 mm bites). Grasping only the plastic portion of the anvil with the large Suture Cut needle driver, while the assist arm 4 and left arm 1 gently splay open the esophageal lumen, the anvil is inserted into the esophagus. The suture is tied down to secure the anvil. A second purse-string suture is placed for reinforcement and “tucking” of redundant tissue folds [Figure 17].

The suture securing the conduit to the diaphragm is cut and the conduit is gently grasped at the tip and retracted cranially. Simultaneous and gentle lateral “lifting” of the conduit at the hiatus can facilitate ease of passage of tubularized stomach and omentum through the hiatus. Grasping of the conduit itself should be avoided when possible to minimize damage to the serosa and/or microvasculature. Proper orientation of the conduit is maintained with the staple line facing approximately towards the lateral chest, and the vascular arcade facing medially towards the mediastinum [Figure 18]. The conduit should be brought into the chest until the previously placed marking suture on the staple line is visible.

A gastrotomy is created at the apex of the conduit parallel to the staple line, large enough to insert the EEA stapler. The robotic left arm and port are removed, the conduit is oriented toward the access incision, and the conduit lumen is irrigated with antibiotic-infused saline. The EEA stapler is inserted through the anterior portion of the access incision along with a laparoscopic grasper and the stapler is passed into the conduit [Figure 19]. The conduit and stapler are brought together into the upper chest and the spike is

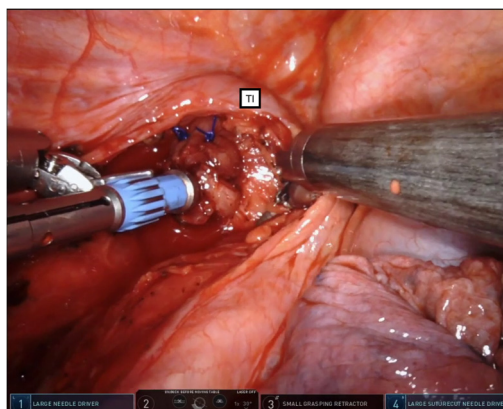


Figure 17. The EEA anvil is inserted into the esophagus and secured with an inner baseball stitch and an outer purse-string stitch. TI: Thoracic inlet.

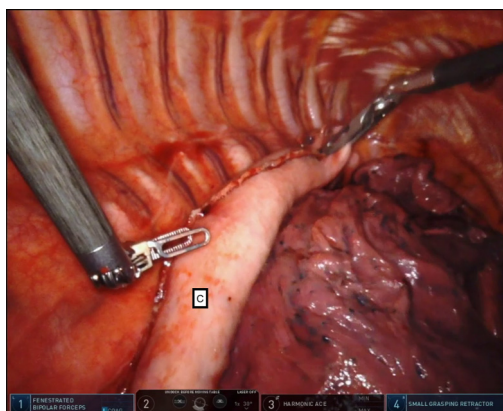


Figure 18. The conduit is advanced cranially with minimal grasping of the conduit. C: Conduit.

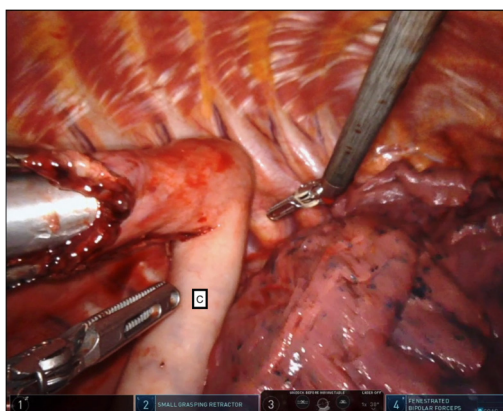


Figure 19. The end-to-end anastomotic stapler is inserted into the chest and passed into the conduit. Careful attention to the proper orientation of the conduit is critical at all times to avoid twisting, torsion, and obstruction. C: Conduit.

deployed through the greater curve of the conduit, ideally at the level of the proximal gastroepiploic arcade [Figure 20]. The spike is docked into the anvil and the stapler is fired [Figure 21]. The anastomotic rings are inspected for completeness and sent to pathology. The robotic left arm (arm 1) is port-hopped to the 12 mm

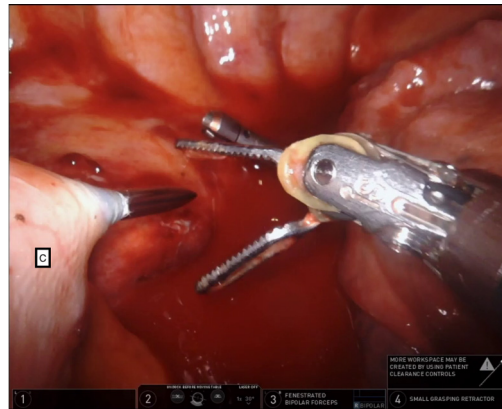


Figure 20. The end-to-end anastomotic spike is deployed through the greater curve of the conduit, ideally at the level of the proximal gastroepiploic arcade. C: Conduit.

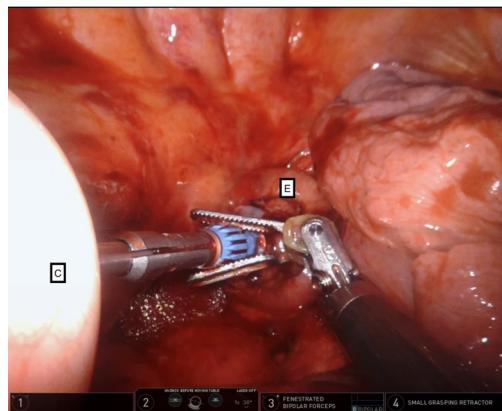


Figure 21. The end-to-end anastomotic spike is docked into its anvil. The stapler is gently approximated, closed, and fired to complete the anastomosis. C: Conduit; E: esophagus.

port to allow for use of the robotic stapler. The proximal tip of the conduit is amputated using a robotic stapler load with care to leave some tissue distance between the new staple line and the circular anastomosis to avoid undue tissue ischemia [Figure 22].

Endoscopy, drains, and flaps

After the anastomosis is completed, intraoperative endoscopy may be performed under thoracoscopic visualization with the chest filled with irrigation to assess for conduit integrity and leak. A nasogastric tube is passed under thoracoscopic visualization before endoscope removal.

If a pedicled omental flap was created (not shown), it is interposed between the anastomosis and the airway, and wrapped around the anastomosis. A 10 mm flat Jackson-Pratt drain (Cardinal Health, Dublin, OH) is placed adjacent and posterior to the anastomosis between the conduit and spine. A 28-French chest tube is placed in the posterior chest and directed towards the apex.

TECHNICAL CONSIDERATIONS

In addition to understanding the sequence of the procedure, some elements of the technique require discussion.

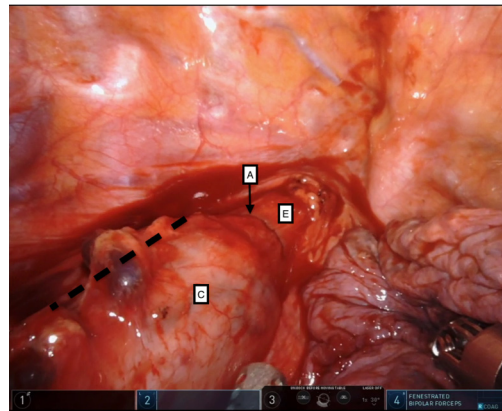


Figure 22. The proximal tip of the conduit is amputated using robotic stapler loads. Although not directly visible in this figure, the dashed line represents the approximate location of the stapled proximal conduit. Note distance (approximately 2 cm) maintained between the anastomotic and conduit staple lines to avoid undue tissue ischemia. A: Anastomosis; C: conduit; E: esophagus.

Benign disease

When operating for a benign indication, the overall conduct of the operation is similar. The major difference is the omission of an aggressive lymphadenectomy. Dissection should stay close to the esophagus for the entire thoracic portion to minimize risk to surrounding structures including the airway and thoracic duct. The conduit length is much more flexible without the need for oncologic margins and can extend further along the fundus. The site of transection of the native esophagus is also flexible, but it should be located at or higher than the level of the azygous vein to avoid excessive reflux. The underlying esophageal pathology may also dictate the level of transection to avoid leaving an excessive nonfunctional esophageal segment in situ.

Learning curve

Although the robotic Ivor Lewis esophagectomy is conceptually similar to a standard minimally invasive Ivor Lewis esophagectomy, it requires the mastery of additional skill sets. Some robotic skills are not directly transferable from prior experience with open or laparoscopic/thoracoscopic surgeries^[31] and require dedicated training. The time to proficiency varies on an individual basis but has been reported between 20^[32] to 70^[33] cases. The initial experience with 100 consecutive cases performed by a single team of two surgeons at Memorial Sloan Kettering Cancer Center identified significantly decreased operative times and surgical complications after approximately 45 cases^[34].

Highlighting the importance of mentorship, surgeons at the University of Utrecht in the Netherlands reduced their time to proficiency by 66% using a structured proctoring program in an established robotic practice^[33]. Conversely, the learning curve for an operation time was not affected when an experienced RAMIE surgeon joined an experienced non-robotic minimally invasive thoracic surgical practice, suggesting the presence of an institutional learning curve in addition to a personal learning curve^[35].

CONCLUSION

As esophageal surgery continues to remain clinically relevant, advances in technology will increasingly evolve the field. Although a relative newcomer to the repertoire of the esophageal surgeon's toolbox, RAMIE is readily establishing itself as a safe and effective approach to esophagectomy^[36-38]. With the expected ongoing development and growing sophistication of robotic platforms, the current and immediate future represents an exciting era in esophageal surgery.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation, and acquisition: Ackerman JM, Sarkaria IS

Provided administrative, technical, and material support: Sarkaria IS, Luketich JD

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Inderpal S. Sarkaria, MD, has received honoraria for consulting and speaking for Intuitive Surgical. James D. Luketich, MD discloses the following: Consultant: Medtronic; CE Speaker's Bureau: Covidien; Stockholder: Intuitive Surgical, Inc., Cigna Corp., and Proctor & Gamble. Dr. Ackerman has no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Patients provided consent for teaching purposes and publication of operative images.

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Case Report

Open Access



Laparoscopic cholecystectomy with indocyanine green fluorescence in patient with situs inversus totalis

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Abstract

Situs Viscerum Inversus (SVI) is a rare autosomal recessive disease. Because of this particular anatomy, it could be challenging for the surgeon to perform any abdominal procedure, including laparoscopic cholecystectomy. In these situations, indocyanine green fluorescence cholangiography can be essential. A 29-year-old female with documented *situs viscerum inversus totalis* underwent laparoscopic cholecystectomy with a four-trocar technique. Switching the vision to the near-infrared camera, which elicited the indocyanine green molecules, the surgeon could easily identify the common bile duct and the cystic duct. Switching back to the normal vision, the operator completed the dissection. The described procedure is still challenging due to the "mirror effect" and the uncommon position of the surgical instruments, especially for right-handed surgeons. Indocyanine green fluorescence angiography can help the surgeon identify the structures in cases of non-regular anatomy such as this.

Keywords: Situs inversus totalis, indocyanine green fluorescence, cholecystectomy

INTRODUCTION

Situs Viscerum Inversus (SVI) is a rare autosomal recessive condition which affects from 1:10,000 to 1:20,000 live births^[1]. Kartagener's syndrome takes place when situs inversus, chronic sinusitis, and bronchiectasis occur together. Two variants are described: situs viscerum inversus partialis (involves thoracic or abdominal organs alone) and situs viscerum inversus totalis (involves both thoracic and



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abdominal organs)^[2]. Because of this particular anatomy, it could be challenging for the surgeon to perform any abdominal procedure, including laparoscopic cholecystectomy^[3]. The “mirror image” is critically confusing, especially during the dissection of the Calot’s triangle. In these situations, indocyanine green fluorescence cholangiography can be essential. It can allow highlighting and safely preserving all the biliary structures^[4,5].

CASE REPORT

A 29-year-old female, BMI 24.2 kg/m², was admitted to the authors’ institution with diagnosed symptomatic presence of stones in the gallbladder with several episodes of epigastric pain, nausea, and vomiting. Medical history showed Kartagener’s syndrome (*DNAH5* gene mutation) with documented situs viscerum inversus totalis, bronchiectasis, and recurrent respiratory infections (the last episode occurring 18 months before the surgery). During a hospitalization in another institution due to bronchopneumonia, the patient underwent CT scan that showed gallbladder stones. Before the surgery, the patient underwent abdomen ultrasound and MRI as well.

The patient underwent laparoscopic cholecystectomy with a four-trocar technique. The operating surgeon was on the right side of the patient and the assistant was between the patient’s legs. First, a 12-mm trocar was placed in the sub-umbilical portion. After inducing the pneumoperitoneum, three 5-mm trocars were placed in the epigastrium, mesogastrium, and left flank, respectively. A diagnostic laparoscopy confirmed the SVI. Twenty-five milligrams of indocyanine green were diluted into 10 mL of sterile normal saline, and a bolus of 0.2 mg/kg was injected intravenously by the anesthesiologist 1 h before the surgery.

During the procedure, the operating surgeon started the dissection of the Calot’s triangle by means of a diathermy hook. Switching the vision to the near-infrared camera, which elicited the indocyanine green molecules, the surgeon could easily identify the common bile duct and the cystic duct. Switching back to the normal vision, the operator completed the dissection. After being isolated, the cystic duct and the cystic artery were clipped, cut, and a retrograde cholecystectomy was performed with no difficulties. The operation took 74 min without intraoperative complications. The patient was discharged on Postoperative Day 2 uneventfully. The final pathology confirmed calculous cholecystitis.

DISCUSSION

The described procedure is still challenging due to the “mirror effect” and the uncommon position of the surgical instruments. For right-handed surgeons, the use of the non-dominant hand to perform the dissection could be challenging. Because of this, surgeons should reflect, first, on the trocars position. Some authors described a simple mirror trocar’s position to perform this surgery^[6], but we suggest reconsidering this simplification for right-handed surgeons and rethinking the use of the instruments. As described in a recent review^[7], there is no standard technique to approach this uncommon orientation. Differently from what is described in other papers^[3,7,8], our equipment was composed by a surgeon and an assistant, and they decided the best port placement that allows the surgeon to perform the dissection with the right hand, having full control of the instrument and completely relying on the assistant for the necessary tractions on the gallbladder to reach the critical view of safety. By this, we tried to avoid the risk of vascular or biliary injury possibly due to the uncommon anatomy.

Thus, the patient’s position was halfway between a mirrored “French” and “American” position because the patient was placed in a lithotomy position but with the surgeon on the patient’s right and the assistant between the patient’s legs. The surgeon’s 5-mm operating trocar was placed midline, between the 5-mm one in the epigastrium and the 12-mm one in the navel. The surgeon was right-handed and used the trocar in

the epigastrium to pull the bottom of the gallbladder upward and the trocar in the mesogastrium to perform the monopolar hook dissection. The assistant, on the other hand, was positioned between the legs to permit holding the scope with the left hand and helping with the right hand the surgeon pulling the infundibulum of the gallbladder outwards. This position allowed the surgeon to obtain the best possible angle to perform a correct dissection of the gallbladder, with easy preparation of the cystic duct and the cystic artery. The administration of ICG (indocyanine green) was carried out about 1 h before the surgery and not previously because, in our department, we try to reduce hospital stays as much as possible we generally hospitalize patients for this type of surgery on the same day of the operation. As suggested by Tebala *et al.*^[9], ICG injection could be performed the day before the surgery in order to reach an optimal concentration in the bile, but there is no clear evidence in the literature that the administration of ICG 1 h before surgery is not already sufficient. This case demonstrated that administration 1 h before surgery could be sufficient, and the images in the video prove it. Indocyanine green fluorescence angiography can help the surgeon identify the structures in cases of non-regular anatomy such as this. In conclusion, in patients with SVI, laparoscopic cholecystectomy can be safely performed and ICG fluorescence can be helpful for identifying anatomical structures.

DECLARATIONS

Authors' contributions

Conception and design: Tirelli F, Grieco M, Biondi A, Belia F, Persiani R

Manuscript writing: Tirelli F, Belia F

Video editing: Grieco M, Tirelli F, Belia F

Final approval of manuscript: Tirelli F, Grieco M, Biondi A, Belia F, Persiani R

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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Is mesh fixation in TAPP and TEP still necessary?

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Abstract

One of the most serious complications after inguinal hernia repair is still the occurrence of chronic pain. The literature describes rates of severe chronic pain of 3%-6%. Laparo-endoscopic inguinal hernia repair is favored to prevent postoperative pain through a minimally invasive approach and sparing of the layers of tissue covering nerves and vessels in terms of reduced risk of damage to these structures. However, the method of fixation of the mesh is still controversial discussed. The use of these penetrating devices such as staples and staplers has been shown to often be complicated by injury to nerves and vessels and occurrence of postoperative pain. The shift to completely atraumatic fixation using adhesives (fibrin glue, cyanoacrylate) began in the early part of this century. Several studies confirmed less postoperative pain after mesh fixation by glue compared to stapler or tacker. Historically, the TEP technique has always been performed without any fixation. Several studies comparing fixation versus non-fixation have been performed in TEP repair and found results with no increase in recurrence rate. Notwithstanding that very few studies comparing fixation versus no fixation with exclusion of large medial inguinal hernias have been published on this topic in TAPP repair, identical results to those with TEP repair were obtained. On the basis of current evidence, no mesh fixation is recommended for laparo-endoscopic inguinal hernia repair except for large medial and combined inguinal hernias. If mesh fixation is required, atraumatic techniques should be used.

Keywords: Laparo-endoscopic inguinal hernia repair, TAPP, TEP, mesh fixation, non-fixation, atraumatic fixation, glue fixation

INTRODUCTION

Since the introduction of minimally invasive techniques in inguinal hernia surgery with TAPP^[1] and TEP^[2],



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mesh fixation has become more and more the focus of discussion. Initially, recurrence rates were the focus of interest, but now the chronic pain rate, which is much higher in percentage terms, is assessed as a measure of surgical success. The type of fixation is closely related to the occurrence of postoperative pain. While penetrating fixation modules such as staplers and staple clips were common in the first era of TAPP and TEP, adhesive techniques have become increasingly popular. This article deals with the background of this development as well as the latest scientific published data and international guidelines and resulting tips and tricks of mesh fixation in laparo-endoscopic inguinal hernia surgery.

Since the implementation of minimal invasive techniques in inguinal hernia repair by TAPP and TEP, the discussion of mesh fixation is still controversially discussed. In the early 1990s, the standard mesh fixation in laparo-endoscopic inguinal hernia repair was performed with staples and tacks^[3]. The use of these penetrating devices was frequently complicated by injury of nerves and vessels and occasionally followed by postoperative pain. Knowledge in terms of the anatomical areas of high risk for injuries to nerves and vessels such as the triangle of doom and pain are well known, but due to the variability of the nerve courses in the region of the inguinal region, a residual risk of injury in the context of a penetrating mesh fixation cannot be ruled out.

In the last two decades, therefore, the mesh fixation techniques have been under discussion. New absorbable fixation models as well as self-fixing meshes have been developed. The advantages of this atraumatic mesh fixation have been investigated in numerous studies and can be found as an evidence-based recommendation in today's guidelines for inguinal hernia care. The completely fixation-free mesh implantation in the TEP technique has been practiced by many TEP surgeons for years because of the extraperitoneal access and the fixation of the mesh resulting from the intraperitoneal pressure immediately after decompression of the pneumoperitoneum. For the TAPP technique, however, there are only a few clinical studies to date. The exact background of the advantages of atraumatic fixation techniques and also fixation-free mesh implantation will be examined in this review.

Pain as main issue in inguinal hernia repair

The recurrence rates after laparo-endoscopic hernia repair have been found to be similar to those with the open mesh techniques, especially with the standard Lichtenstein technique. However, the advantage of lower pain incidence after TAPP and TEP compared to Lichtenstein repair became apparent very soon. In a recently published meta-analysis and trial sequential analysis of primary unilateral uncomplicated inguinal hernias comparing open versus laparo-endoscopic mesh repair, the current situation of postoperative pain and recurrence was described at length and analyzed in detail^[4]. This study enrolled 12 randomized controlled trials (RCT) with 3966 patients randomized to Lichtenstein repair ($n = 1926$) or laparoscopic repair ($n = 2040$). No significant differences were detected in recurrence rates between the laparoscopic and open groups [odds ratio (OR) 1.14, 95%CI: 0.51-2.55, $P = 0.76$]. Laparo-endoscopic repair was associated with reduced rate of acute pain compared to open repair (mean difference 1.19, 95%CI: - 1.86 to - 0.51, $P \leq 0.0006$) as well as reduced chronic pain compared to open (OR 0.41, 95%CI: 0.30-0.56, $P \leq 0.00001$). A trial sequential analysis found that further studies are unlikely to demonstrate a statistically significant difference between the two techniques. This meta-analysis concluded that laparo-endoscopic repair has a statistically significant advantage in inguinal hernia repair in comparison to open mesh repair in terms of postoperative pain, and it complies with the current Hernia Surge Guidelines.

Why traumatic mesh fixation in laparo-endoscopic inguinal hernia repair should be abandoned?

In the early 1990s, the laparoscopic techniques of TAPP and TEP were developed. In addition to the discussion about mesh, questions with regard to size and fixation with a stapler or tacker were standard. The only recommendation at that time was to avoid the region caudal to the ilio-pubic tract, known as the

triangle of doom and pain, for penetrating fixation modules^[1].

Since Reinbold's anatomical study^[5], we know that the entry points of the genital and femoral branch of the genitofemoral nerve have a great variability and can lie above the ilio-pubic tract. This widens both the triangle of doom and the triangle of pain. This also significantly increases the risk of nerve injury when using penetrating fixation models. Similarly, the varied course of the ilio-hypogastric nerve, which can also be injured during traumatic mesh fixation in TEP and TAPP repair, must also be taken into account.

In conclusion, a significantly increased risk of injury must be calculated for traumatic mesh fixation techniques, which leads to the fact that only atraumatic mesh fixation methods are recommended in the international guidelines for the laparo-endoscopic treatment of inguinal hernias^[6].

Is the use of resorbable tacker able to prevent chronic postoperative pain?

Initiated by the results of comparative studies on different mesh fixation devices, the hypothesis arose that the re-absorbability of penetrating staples could solve the problem of nerve damage, starting from neuropraxia to total dissection. By definition, the chronicity of pain appears after 3-6 months at the latest and is compared to the resorption time of these fixation models of 6-8 months. Thus, this consideration was based on lacking knowledge of the time course of a nerve injury and entrapment. Moreover, the configuration of these resorbable staples was partly incompatible with regard to the size of the mesh pores to be considered and the depth of penetration especially in laparoscopic incisional and ventral hernia repair.

In summary, the problem of penetrating fixation models is not solved by the absorbability of the material used^[7,8] and makes no difference in outcome results such as postoperative pain and recurrence.

Seroma

The incidence of postoperative seroma formation in laparo-endoscopic inguinal hernia surgery is reported in the literature to be between 3.0 and 8% for TAPP and between 0.5% and 12.3% for TEP. A clinical association was reported with large hernia sacs in direct and indirect inguinal hernias but also with mesh fixation^[9]. In a registry study by Köckerling *et al.*^[10], the occurrence of seroma formation after TAPP treatment was analyzed in relation to the type of fixation and the type of hernia. In the multivariate analysis, adhesive fixation had a twofold risk of postoperative seroma formation compared to staple fixation and a 5-fold risk compared to non-fixation. In relation to hernia defect, M3 (direct inguinal hernia, defect size ≥ 3 cm, EHS classification) had a 2.8-fold increased risk compared to M1 (direct inguinal hernia, defect size ≤ 1.5 cm, EHS classification) inguinal hernia, and direct inguinal hernia had a 1.2-fold increased risk compared to indirect inguinal hernia.

The closure of the direct inguinal hernia defect area of the type MIII inguinal hernia by means of inversion of the dilated transversalis fascia within laparo-endoscopic hernia repair to avoid postoperative seroma formation seems recommendable. The use of barbed suture material for this purpose seems to be suitable. The results of a RCT by Zhu *et al.*^[11] showed a significantly reduced incidence and volume of seroma formation without increasing the risk of recurrence, acute and chronic pain.

In another prospective study by Usmani *et al.*^[12] comparing direct defect closure in MII and MIII inguinal hernias by barbed non-resorbable suture versus non-closure in TEP and TAPP repair demonstrated a statistically significant reduction not only in seroma formation (12.6% vs. 6.4%, $P = 0.045$) but also in recurrence (4.4% vs. 0.9%, $P = 0.036$) after a follow-up of at least 9 months.

The advantage of direct defect closure in prevention of recurrence was also reported in a retrospective study by Ng *et al.*^[13] in TAPP and TEP repair using interrupted non-resorbable single sutures for MII and MIII inguinal hernias with a 6.4% recurrence rate in the non-closure group vs. 0% in the closure group after 1 year. In both studies^[12,13], besides the defect closure, mesh fixation was performed by resorbable tackers.

In another prospective study by Clout *et al.*^[14] patients were treated with Endoloop closure by long term absorbable suture for MII or MIII direct defects in TEP repair. The meshes were fixated using fibrin sealant only. After a median follow-up of 5.9 years, there was no recurrence.

In summary, no mesh fixation clearly has the lowest seroma rate in laparo-endoscopic inguinal hernia surgery. But most of the studies with non-fixation of mesh excluded large direct inguinal hernias.

The defect closure respectively reducing the dilated transverse fascia by suture in MII and MII direct inguinal hernia in combination with mesh fixation by tackers or glue seems to prevent not only postoperative seroma formation but moreover the risk of recurrence.

Since atraumatic mesh fixation reduces the risk of postoperative pain, the combination of defect closure and mesh fixation by glue or the use of self-fixing meshes in MII and MIII direct inguinal hernias seems recommendable.

GLUE FIXATION IN TEP AND TAPP

Fibrin glue

Starting with the first experimental study by Katkhouda *et al.*^[15] by using fibrin glue for mesh fixation in TEP repair, atraumatic fixation was born. Fibrin glue, known as Tissel[®] or Tissucol[®] (Baxter Healthcare, Deerfield, IL, USA), is a biologic hemostatic agent consisting of human fibrinogen and thrombin. In an experimental study, Schwab *et al.*^[16] carried out a biomechanical analysis of mesh fixation in TAPP and TEP comparing non-fixation versus suture versus fibrin sealant fixation. Glue fixation obtained the highest stress resistance compared to non-fixation and suture fixation. Regarding the application of fibrin sealant in laparo-endoscopic inguinal hernia repair, a spray-application at 1.5 bar pressure and a dose of approximately 0.014 mL/cm² to achieve a thin layer with broad coverage of mesh and efficient trans-porous contact with the underlying tissue is recommended^[17].

After the first clinical publication by Langrehr *et al.*^[18] in 2005, several RCTs followed with fibrin fixation of mesh versus stapler and tackers fixation techniques in TAPP^[18-22] and TEP^[23-26] surgeries. The rate of postoperative pain was predominantly significantly lower compared to the penetrating fixation techniques without increased recurrence rates.

The systematic review and meta-analysis comparing fibrin glue versus staple mesh fixation in TAPP by Shi *et al.*^[27] including four RCTs detected no significant difference in hernia recurrence OR 2.10, 95%CI: 0.61-7.22, seroma or hematoma formation (OR 0.55, 95%CI: 0.27 to 1.14) and operating time (SMD 0.80, 95%CI: -0.34 to 1.94). Another systematic review and meta-analysis, by Sajid *et al.*^[28], with the inclusion of 5 RCTs found no significant difference regarding operating time, postoperative pain, postoperative complication, length of hospital stay and risk of recurrence, but a lower risk of chronic pain.

Kaul *et al.*^[29] published a systematic review and meta-analysis comparing fibrin glue and staple fixation in TEP. In the four enrolled studies, no difference in inguinal hernia recurrence with fixation of mesh by staples/tacks versus fibrin glue (OR 2.13; 95%CI: 0.60-7.63) was found. The incidence of chronic pain at 3

months was significantly higher with staple/tack fixation (OR 3.25; 95%CI: 1.62-6.49). Whereas no significant difference was seen in operative time, seroma formation, hospital stay, or time to return to normal activities.

In summary the use of fibrin glue for mesh fixation in TAPP and TEP is a safe atraumatic fixation technique and provides less chronic pain incidence compared to traumatic fixation.

The optimal application method is the spray technique to generate a thin adhesive layer.

Cyanoacrylates

Besides the biological fibrin glue, a synthetic cyanoacrylate (CA) is an alternative glue material. One of the most serious problems of the surgical use of CAs involves its degradation and toxicity. The main toxic products released by the degradation of CA alkyl chains are formaldehyde. A second basic problem associated with CAs is the flexibility. After polymerization, these polymers become hard and brittle, which might be counterproductive for tissue conditions^[30]. In an *in vivo* preclinical study by Pascual *et al.*^[31] CAs currently used in clinical practice, with different alkyl chain lengths, Ifabond (n-hexyl), Glubran (n-butyl), and OCA (n-octyl) obtained sufficient tissue integration, proper mesh fixation and effective short-term biocompatibility. CA (n-octyl) revealed the lowest seroma formation macrophage response.

The largest number of mesh fixations by CAs (n-butyl) in TAPP repair was published by Kukleta *et al.*^[32] showing excellent results in terms of biocompatibility and risk of recurrence. The technique recommended by these authors for CA mesh fixation consists in applying just a few drops each to all four quadrants of the mesh. Subwongcharoen *et al.*^[33] reported on a RCT comparing staple fixation versus CA (n-butyl) in TEP repair. Postoperative pain assessed by VAS was significantly higher in the staple group after 24 hours (1.6 +/- 1.33 vs. 2.35 +/- 1.32) ($P = 0.037$). The rate of chronic pain after 3 months and 1 year was higher in the staple group but did not reach significance. Complications rates and recurrences after one year were not significant.

In summary, cyanoacrylate, preferably n-octyl cyanoacrylate, is safe to use for adhesive fixation of meshes in TAPP and TEP. Care should be taken to ensure sparing spot application. This is in contrast to the large-area trans-porous spray application of fibrin glue, which achieves elastic fixation of the fibrin glue^[34].

Self-fixating mesh

So far, in contrast to the open mesh methods, there are only a very few publications for the use of self-fixating mesh. In feasibility studies with the use of self-fixation mesh in TAPP by Birk *et al.*^[35] and Li *et al.*^[36] in TAPP and TEP and by Bresnahan *et al.*^[37] in TEP, only one RCT by Denham *et al.*^[38] was published in 2019. In this study 217 patients with primary, unilateral inguinal hernias were randomized to non-self-fixation or self-fixation group in TEP repair. A subgroup randomization was performed on the self-fixating mesh group with direct hernias > 2 cm ($n = 38$). Fifty percent of this group ($n = 19$) were randomized to receive tackler fixation. The median operative times and length of hospital stay were similar. More patients in the non-fixating mesh group received tacks (43 vs. 19, $P = 0.001$). During the first 3 postoperative days non-fixating mesh patients reported significantly less pain, whereas 3 weeks or 1 year postoperatively no significant difference was detected. In the follow-up of one year, no recurrence was found in either of the groups. A subgroup analysis of direct inguinal hernias could not be performed due to the low number of patients. In conclusion, the authors stated that “self-fixating mesh does not appear to positively impact QoL after TEP repair”.

Since the evidence regarding the benefit using self-fixating meshes in laparo-endoscopic inguinal hernia repair is too little, no conclusions or recommendations can be derived at present.

Is there a need for mesh fixation in TEP or TAPP?

Finally, the main topic of this paper is the discussion of non-fixation of mesh in laparo-endoscopic inguinal hernia surgery.

The first study in terms of non-fixation in TEP repair in an experimental setting by Katkhouda *et al.*^[15] demonstrated the risk of mesh movement. Despite this finding and an increased potential risk of early recurrence derived from it, the non-fixation in TEP technique, for the difference of TAPP, has been thematized very early. The obvious reason for this was the specific technique of implanting the mesh in a pocket that made it unlikely that the mesh would slip after the pneumoperitoneum was depressurized. On the other hand, the advantage of not fixing the meshes is associated with a significantly reduced risk of seroma occurrence^[10].

In a study by Claus^[39] specifically focused on mesh displacement in the absence of fixation in TEP repair, only a minimal displacement was found. The comparison of radiologically controlled mesh movement after bilateral versus unilateral TEP repair showed 30 days postoperatively a median of 1.9 and 1.8 cm ($P = 0.78$), respectively. With this aspect of potential, albeit minor mesh displacement, care must be taken to ensure adequate size and defect overlap, especially in large direct inguinal hernias.

In 1999, Ferzli *et al.*^[40] published the first study comparing tackler versus non-fixation in TEP repair without significant differences in recurrence or complication rates after a 12-month follow-up.

Since then, several studies^[41-46] and meta-analyses^[47-49] of TEP procedures with non-fixation were published. The conclusion of these were that outcomes after non-fixation in TEP repair are comparable to fixation and not associated with higher recurrence rates. However, the various meta-analyses had a certain bias due to the inclusion of RCTs with recurrent surgery, bilateral inguinal hernias, both sexes and exclusion of large medial inguinal hernias. As there has been no RCT on primary unilateral inguinal hernias to date, an evidence-based statement can only be drawn to a limited extent.

Based on the Swedish Hernia Registry, a study including 1110 male patients undergoing TEP repair comparing permanent fixation versus non-fixation including glue fixation in terms of chronic pain detected no significant difference^[50]. Going into detailed analyses, the rate of permanent fixation was significantly higher in medial hernias compared to non-fixation and glue fixation ($P < 0.003$) as well as regarding the defect size ($P < 0.002$). The distribution of unilateral inguinal to bilateral and recurrent inguinal hernias was 36, 64 and 9%, respectively. The use of heavy meshes were significantly more frequent in the fixation group compared to non-fixation and glue-fixation ($P < 0.015$). In a subgroup-analysis, the use of glue fixation was performed significantly more in medial hernia compared to non-fixation ($P < 0.001$). After a median follow-up of 7.5 years, a total of 15 patients had an operation for recurrent hernia: 1.5% for fixation and 1.3% for non-fixation and glue-fixation ($P < 0.735$). Looking to the sub-analysis of recurrences after medial hernia repair, no significant difference was seen (0.7% after fixation vs. 1.7% after non-fixation and glue-fixation; $P < 0.669$). In a multivariable analysis, the risk factor for chronic pain was a postoperative complication.

In summary, in this registry study of TEP repair in male patients, a low incidence of recurrence was observed with no significant difference seen in non fixation, permanent and glue fixation. The conclusion of this study suggests that non-fixation in TEP repair does not carry a risk of recurrence even in medial

hernias. Nevertheless, the subgroup analysis shows that glue-fixation in medial hernias was significantly more frequently used compared to non-fixation. Since no evaluation is available regarding the size and type of fixation of medial inguinal hernias, the interpretation in this regard should also be viewed with caution.

For the TAPP procedure, only 2 RCTs^[51,52] comparing non-fixation with staple fixation have been published to date. In 1999, Smith *et al.*^[51] reported a recurrence rate after median follow-up of 16 months (range, 1-32 months) of 0% after non-fixation and 1% after staple fixation without significant difference ($P = 0.09$). Furthermore, no significant difference was detected in operative time and chronic pain between the two groups. Limitations of this study have to be considered regarding the short time of follow up and the number of patients followed up of only 65% by examination and 22.2% by telephone. In the study by Li *et al.*^[52], male patients with primary, unilateral inguinal hernia, defect size < 4 cm diameter were randomly allocated to non-fixation or staple fixation. After a median follow up of 11.5 months after non-fixation and 11.2 months after staple fixation, no recurrences were found. Postoperative VAS pain scores up to 6 months for the non-fixation group were significantly lower than in the fixation group. The quality of life regarding physical function, physical role, bodily pain, and general health in the non-fixation group was significantly better than in the fixation group. This RCT also had limitations regarding the very short follow-up period and the inclusion criterion restricted to smaller than 4-cm defect size.

In summary, the question of non-fixation in TEP and TAPP has limited answerability. The lowest common denominator for low-risk non-fixation of meshes in TEP and TAPP techniques seems to be primary unilateral male inguinal hernias with exclusion of medial hernia types with a defect diameter of ≥ 3 cm.

Discussion

The appropriate technique in TEP and TAPP repair is the most important requirement of prevention of postoperative pain. The dissection in the right plane with preserving the protective layers such as spermatic sheath to prevent nerve injury and to avoid any coarse grasp of the spermatic cord are basic rules to be observed. The preparation of the landing zone has to be sufficient for a mesh implantation of at least 10 cm by 15 cm. In the special case of direct hernia with a defect size of 3 cm and more the mesh size has to be larger, e.g., 12 cm by 17 cm to guarantee a sufficient overlap of at least 3 cm over the midline. In addition, the inversion of the dilated transverse fascia seems to prevent postoperative seroma occurrence in these cases. Following these crucial steps of TEP or TAPP are mandatory to achieve best outcomes regarding postoperative pain and recurrence rate.

The choice of the optimal mesh for laparo-endoscopic inguinal hernia repair has been discussed for years with the question of light or heavy weight. Until recently, lightweight meshes were clearly preferred in terms of pain and reduced foreign body reaction, but an RCT with long-term results has changed the evidence^[53]. In this 5-year follow-up RCT study in TEP repair of primary unilateral inguinal hernias, the recurrence rate was significantly increased after the use of lightweight mesh (UltraPro[®]) compared to the use of heavyweight mesh. This publication did not remain uncommented^[54]. Since the classification of medial hernias in this study is based on the Nyhus classification^[55] and not on the EHS classification^[56] with differentiation of defect sizes (MI, MII and MII), the MIII hernia cannot be evaluated selectively.

The studies, already mentioned in the seroma chapter regarding the closure or shortening of the dilated transverse fascia have not only led to a reduction in seroma formation but also to a decrease of the recurrence rate. This relationship seems quite plausible. Considering the bending stiffness of small pore-sized/heavyweight meshes compared to large pore-sized/lightweight meshes, significant differences can be found, which are especially important when there is no tissue directly under the mesh but an empty space.

In the biomechanical study by Hollinsky *et al.*^[57], the ultimate tensile strength and elasticity in association with defect size of 1.5, 3 and 5 cm was assessed by the use of a lightweight mesh in comparison to a heavyweight mesh. Regarding 1.5 cm of defect size no difference was seen, but in case of defect size 3 and 5 cm, the lightweight mesh flexed 3.16 +/- 0.4 mm and 10.4 +/- 2.5 mm significantly more in comparison to the heavyweight mesh 0.34 +/- 0.2 mm and 3.97 +/- 0.7 mm ($P < 0.001$). This study is of main importance to understand biomechanical relationships of mesh properties and defect size.

While meta-analyses to date have shown advantages for the use of lightweight meshes in laparo-endoscopic inguinal hernia surgery^[58], the inclusion of the TEP study by Ross *et al.*^[53] changed the recommendation not to use lightweight meshes, especially in direct hernias, due to the increased risk of recurrence (RR 2.21; 95%CI: 1.14-4.31), especially in non-fixated mesh direct repairs (RR 7.27; 95%CI: 1.33-39.73) and/or large hernia defects^[59]. No significant differences were determined in terms of pain and foreign body sensation. Similar results were found in the meta-analysis of Hu *et al.*^[60].

If you look at the EHS update guidelines from 2014^[61], you will find the recommendations for mesh fixation in TEP if a heavyweight mesh is used: traumatic mesh fixation should be avoided except in large direct inguinal hernias. For TAPP treatment, atraumatic mesh fixation without increased risk of recurrence within one year was recommended.

Nowadays, in the nomenclature of mesh properties, light and heavy are obsolete; rather, effective porosity and surface properties as well as elasticity are some of the defining properties of meshes. However, there is a complex interplay between the polymer, textile structure, amount of material, porosity, processing of the material, position and mechanical load on the mesh.

Despite some limitations of the available evidence, the HerniaSurge Group stated in the current guidelines^[6] that mesh fixation is not required in almost all types of inguinal hernias in TEP repair. However, a strong recommendation for mesh fixation was made for large medial inguinal hernias (MIII in the EHS classification) for TAPP and TEP repair. If fixation is required, the HerniaSurge guidelines recommend an atraumatic technique to reduce the risk of early postoperative pain.

In a Herniated register study, 11,228 male patients with primary unilateral inguinal hernia underwent TAPP technique and were followed up for 1 year. In this study published by Mayer *et al.*^[62], mesh fixation was performed in a total of 66.1% of the procedures. In the unadjusted analysis, there was no significant difference in recurrence rate (0.88% with fixation vs. 1.1% without fixation; $P = 0.259$). In a multivariable analysis of all potential influencing factors such as age, ASA, BMI, risk factors, defect size, mesh fixation, location of the defect and mesh size, no factor was identified to influence the recurrence rate at 1-year follow-up. However, for medial and combined defect localization in comparison to lateral localization, a highly significant effect was detected ($P < 0.001$). Using mesh fixation and larger meshes, it was possible to significantly reduce the recurrence rate for larger medial hernias in this series ($P = 0.046$). This registry study clearly confirms the need of mesh fixation for MIII inguinal hernias, as recommended by the HerniaSurge Guidelines, but also for combined inguinal hernias and impressively demonstrates the advantage of using larger implants for recurrence prevention.

CONCLUSIONS

The central question of fixation or non-fixation of mesh in laparo-endoscopic inguinal hernia management can only be viewed and answered on a multifactorial basis. According to the existing literature, it is recommended that mesh fixation should be performed in case of medial as well as combined inguinal

hernias. The inversion of dilated parts of the transverse fascia in M III inguinal hernias to prevent the formation of seroma and recurrence, as well as the implantation of larger meshes, also seems to be preferable in this constellation. In contrast, the use of ultra-lightweight, large-pored meshes without mesh fixation does not seem to be appropriate in this indication. For all other types of inguinal hernias, mesh fixation can be omitted but always under the condition that all standards of laparo-endoscopic inguinal hernia management are met.

DECLARATIONS

Authors' contributions

All substantial contributions to the concept and design of this review, performed literature search, interpretation and conclusions: Fortelny RH

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Conflicts of interest

Dr. Fortelny reports receipt of honoraria from BD BARD and B.Braun for speaking services.

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Review

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Endoscopic endonasal surgery for anterior skull base meningiomas

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Abstract

Meningiomas of the tuberculum sellae, planum sphenoidale and olfactory groove region are relatively common. Traditionally these meningiomas have been approached through several transcranial approaches. More recently, keyhole approaches have been utilized with success even for large tumors. Endoscopic approaches are an extension of this philosophy, which, in carefully selected patients, may be an excellent alternative, offering a direct line of site from an endonasal approach without brain retraction. Furthermore, bilateral optic canal decompression can be safely and effectively accomplished. We propose that a majority of tuberculum sellae and posterior planum meningiomas may be removed via an endonasal approach, particularly those that are 3 cm or smaller in maximal diameter with minimal lateral extension beyond the supraclinoid carotid arteries and with medial optic canal invasion. A deepened sella is also a favorable factor for endonasal removal. In contrast, we propose that a minority of olfactory groove meningiomas are ideal candidates for endoscopic trans-cribriform removal given the higher risk of anosmia and cerebrospinal fluid leak via the nasal corridor. Instead, a majority of these tumors can be safely and effectively removed via a transcranial keyhole approach, such as the supraorbital “eyebrow” craniotomy or traditional pterional craniotomy with a higher rate of olfaction preservation.

Keywords: Meningioma, endoscopy, anterior skull base, tuberculum sellae, planum sphenoidale, olfactory groove, optic canal decompression

INTRODUCTION

The era of endoscopic transsphenoidal surgery began in the late 1990s, bringing with it improvement of



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illumination, image quality, viewing angle and dexterity over previous microscopic approaches. Since then, endonasal techniques have expanded into both sagittal and coronal planes, including the anterior skull base^[1-8]. This region endoscopically is defined posteriorly by the tuberculum sellae, anteriorly by the posterior table of the frontal sinus, and laterally by the junction of the lamina papyracea and the fovea ethmoidalis. The major divisions from anterior to posterior are the cribriform plate, planum sphenoidale and tuberculum sellae, all of which are accessible with the use of straight or angled endoscopes.

Anterior skull base meningiomas are relatively common, with tuberculum sellae/planum sphenoidale representing approximately 5%-10% of all meningiomas, and olfactory groove 8%-13%^[6]. Tuberculum sellae/planum sphenoidal meningiomas frequently exhibit growth patterns that displace the optic nerves and chiasm posteriorly and/or superiorly. Optic canal invasion is present in approximately two thirds of cases^[9]. This growth pattern results in relatively early detection with small size. Olfactory groove meningiomas, on the other hand, generally are much larger when at presentation due to initial lack of critical mass effect on orbitofrontal cortex.

Traditionally, frontal fossa meningiomas have been approached through several transcranial approaches, including frontal, bifrontal and pterional craniotomies. More recently, keyhole approaches, such as the supraorbital craniotomy, have been utilized with success even for very large tumors^[10,11]. Endoscopic approaches are an extension of this minimally invasive keyhole philosophy and, in carefully selected patients, they may be an excellent alternative due to the midline location of these tumors, offering a direct line of site from an endonasal approach without brain retraction^[5,6,8,12-14]. Furthermore, bilateral optic canal decompression can be safely and effectively accomplished in patients with compressive optic neuropathy from tumor extension into the medial optic canals^[15-17].

Here we describe both the transplanum/transtuberculum and transcribriform approaches for anterior skull base meningiomas, including the indications, limitations and outcomes. We propose that a majority of tuberculum sellae and posterior planum meningiomas can be removed with an endonasal approach given the superior access to the medial optic canals. In contrast, only a minority of olfactory groove meningiomas are ideal for the endonasal route given that the transcribriform approach will inevitably lead to anosmia in the vast majority of patients. In fact, recent systematic reviews by Shetty *et al.*^[18] and Yang *et al.*^[19] of studies comparing transcranial and endoscopic approaches for tuberculum sellae/planum sphenoidale and olfactory groove meningiomas, respectively, found that 39% of the former are performed endoscopically vs. only 19% for the latter. We also emphasize that the supraorbital “eyebrow” craniotomy is an excellent and complimentary alternative for anterior skull base meningiomas^[10].

TRANSPALM/TRANSTUBERCULUM APPROACH FOR TUBERCULUM & POSTERIOR PLANUM MENINGIOMAS

Patient selection & surgical considerations

The optimal approach for symptomatic tuberculum sellae meningiomas remains controversial. While conventional transcranial approaches are still widely used, minimally invasive “keyhole” approaches are increasingly applied, but the ideal approach remains debated^[11,13,20-27]. We and others have used the endoscopic endonasal approach and supraorbital “eyebrow” approach, depending on certain tumor characteristics for over 15 years. In our initial experience addressing this topic published in 2009 and using an endoscope-assisted method, we concluded the endonasal route was preferred for smaller meningiomas that did not extend beyond the supraclinoid internal carotid arteries (ICAs), while larger tumors that extended more laterally were appropriate for supraorbital removal^[11]. During this time period, we approached 75% of tuberculum sellae meningiomas by the supraorbital approach and 25% by an endoscope-

assisted endonasal approach. Since 2009, we have transitioned to a fully endoscopic endonasal approach while gaining more experience with the supraorbital route for parasellar tumors and have reversed the ratio to 61% endoscopic endonasal and 39% supraorbital route^[2,10,28-30].

There are several major advantages of the endonasal route. The natural nasal corridor provides a direct trajectory to the tuberculum sellae and posterior planum, facilitating tumor removal with minimal brain manipulation. The meningioma lies between the surgeon and critical structures such as the optic nerves, optic chiasm and ICAs, thereby minimizing risk of iatrogenic injury. Medial optic canal decompression can be safely and effectively performed when optic canal invasion is present. Devascularization is accomplished early in surgery by interrupting the dural blood supply during the approach. Finally, adjacent hyperostotic bone is readily removed *en route* to the meningioma.

When selecting patients for an endoscopic endonasal transplanum/transtuberculum approach, the following factors are considered favorable: (1) smaller (≤ 3 cm), relatively midline tumors with minimal-to-no lateral extension beyond the supraclinoid ICAs; (2) the majority of tumor below the planum; (3) presence of tuberculum sellae hyperostosis; (4) relatively acute tuberculum angle (less than 135°); and (5) unilateral or bilateral medial optic canal invasion [Figure 1]. The endonasal corridor has limited access lateral to the supraclinoid ICAs, so gross total removal of larger tumors, or those with further lateral extension, may not be possible. When the majority of the tumor lies below the level of the planum sphenoidale, a portion of the tumor will often not be visible with a transcranial approach. In contradistinction, the endonasal approach affords a direct view of the sella, enabling complete tumor resection. This is especially true in the presence of a relatively acute tuberculum angle. Similarly, hyperostosis of the tuberculum sellae may further limit visualization of the inferior aspect of the tumor in a transcranial approach, so an endonasal approach should be favored when this feature is present. Finally, optic canal invasion often occurs along the inferomedial aspect of the canal. Transcranial approaches are limited in their ability to access this region on the ipsilateral side. However, bilateral optic canal decompression is easily performed from an endonasal approach. Direct visualization of the tumor invading the optic canals is obtained, enabling safe removal. In our experience, 71% of patients with vision deficits experienced objective improvement after an endoscopic endonasal transplanum/transtuberculum approach for meningioma, with no instances of vision worsening^[30].

In addition to the aforementioned factors, several important pre-operative considerations should be made. The surgical goal must be clearly defined *a priori*. Vascular encasement should be identified, with a consideration for subtotal resection or transcranial approach if present. Similarly, optic nerve encasement is generally not conducive to achieving gross total resection. A conchal or presellar sphenoid sinus pneumatization pattern may make identification of critical landmarks difficult. A medial course of the cavernous, clinoid or supraclinoid segments of the ICAs may significantly limit the surgical corridor. The endonasal approach creates a large dural defect requiring a robust skull base reconstruction, ideally with a pedicled nasoseptal flap and multilayered reconstruction. Thus, careful planning is required for all patients, particularly those at a high risk of cerebrospinal fluid (CSF) leak, such as patients with high body mass index, uncontrolled diabetes, previous surgery and/or previous radiation therapy.

The goals of surgery for the endoscopic endonasal transplanum/transtuberculum approach for tuberculum sellae meningiomas are: (1) maximal safe resection; (2) decompression of the optic apparatus when applicable; (3) preservation and/or restoration of normal pituitary gland function; (4) effective reconstruction of the skull base; and (5) avoidance of complications.

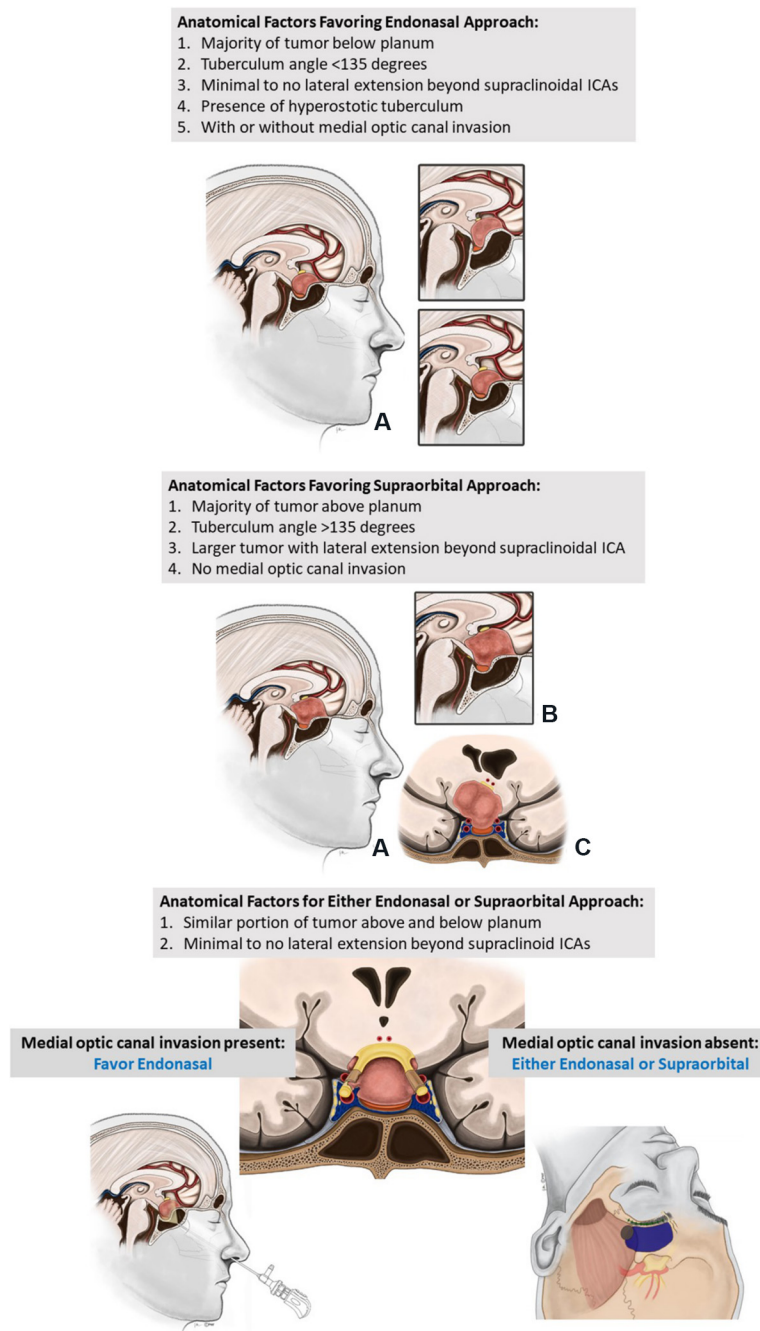


Figure 1. Algorithm for approaching tuberculum sella meningiomas with 4 possible scenarios. In A the endonasal route is preferred; in B the supraorbital is favored, and in C either approach may be reasonable based on tumor location, parasellar anatomy and presence or absence of optic canal invasion. Overall, a slight majority of these tumors are now approached by the endonasal given a high propensity of tuberculum meningiomas to invade one or both medial optic canals. ICAs: Internal carotid arteries.

Pre-operative management

Patients considered for surgery should undergo a detailed history and neurological exam. This evaluation should include assessments of mental status, cranial nerve function, visual acuity, visual fields, dilated fundoscopic evaluation, optical coherence tomography, comprehensive endocrinological evaluation (if the tumor encroaches on the sella) and endoscopic nasal examination. Thin slice CT is recommended to

evaluate the relevant paranasal sinus and skull base bony anatomy, sphenoid sinus pneumatization pattern, areas of dehiscence and presence of hyperostosis. MRI should be thoroughly examined for tumor origin, extension, and localization critical structures in relation to the tumor such as the optic nerves and chiasm, ICAs and their branches, pituitary gland and infundibulum. Either CT or MR angiography may be indicated for tumors that encase the vasculature for the purposes of surgical planning [Figures 2-4].

Surgical technique

At our center, the endoscopic endonasal transplanum/transtuberculum approach is performed as a binostril technique with a neurosurgeon and otolaryngologist working together throughout the majority of the procedure. The operation is begun with a 4 mm 0° rigid high-definition endoscope, with 30° and 45° endoscopes available for use later in the procedure. Surgeon ergonomics are addressed by positioning a high-definition monitor directly in front of each surgeon. A third monitor for neuronavigation is placed between the 2 high-definition monitors [Figure 5]. Surgical steps are detailed in Video 1.

Patient positioning

The patient is positioned supine with the head tilted toward the left shoulder and turned 20° to 30° toward the right. For an approach to the planum sphenoidale/tuberculum sellae, 10° to 15° of extension is used and the head is fixed in the three-point Mayfield cranial fixation system. Optical neuronavigation is registered and leads for somatosensory evoked potential monitoring are placed. The right lower quadrant of the abdomen is prepped for a fat graft harvest.

Nasal preparation and approach

The nasal cavity is prepared prior to beginning the approach by spraying oxymetazoline in both nares. The face, perinasal area, and right lower abdominal area (for fat graft harvesting) are then prepped and draped in a sterile fashion. We have recently implemented a nasal rinse with a betadine solution diluted 1:1 with normal saline to minimize the risk of COVID-19 transmission.

The initial approach into the sphenoid sinus is performed by the otolaryngologist with the 0° endoscope. Lidocaine 1% with 1:100,000 epinephrine is first injected into the middle turbinates and posterior nasal septum bilaterally. Both inferior turbinates are first in-fractured then out-fractured. Similarly, the middle turbinates are out-fractured, exposing the sphenoid ostia. Next, monopolar electrocautery with a curved microtip is used to make a unilateral mucoperiosteal incision beginning immediately inferior to the sphenoid ostium and extending to a point approximately 2 cm anteriorly, along the inferior vomer and posterior nasal septum, before turning superiorly towards the olfactory groove [Figure 6]. The rescue flap is elevated inferiorly and the septal olfactory strip above is elevated superiorly, preserving the olfactory fibers. A nasoseptal flap is harvested on the contralateral side, ensuring the preservation of the septal olfactory strip by using a similar mucoperiosteal incision that is carried laterally into the inferior meatus to harvest a sufficiently wide flap. The nasoseptal flap is placed in the nasopharynx and kinking of the vascular pedicle is avoided.

Next, a posterior septectomy is performed to connect the right and left nasal cavities. An attempt is made to remove the bone in one piece to preserve the bone for skull base reconstruction. A wide sphenoidotomy is then performed that extends lateral to the sphenoid ostia and generally to the floor of the sphenoid sinus inferiorly and to the roof of the sphenoid/ethmoid junction superiorly. Using a 30° endoscope, the ethmoid air cells are opened bilaterally to expose the laminae papyraceae and each septal olfactory strip is lateralized along their respective fovea ethmoidalis. All mucosa of the sphenoid sinus is removed to facilitate adherence of the nasoseptal flap at the conclusion of the procedure.

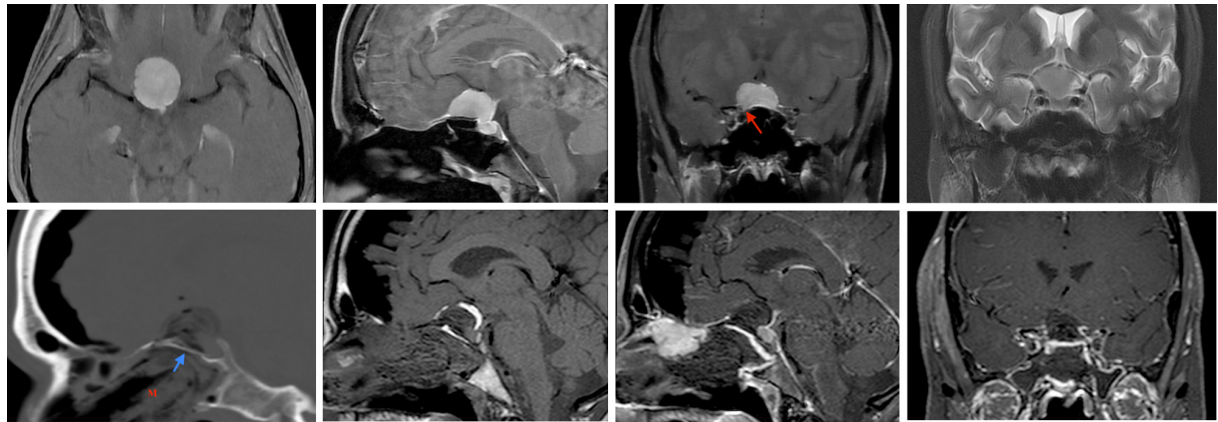


Figure 2. A 52-year-old woman presented with progressive bilateral vision loss, right worse than left, over three years. (Top row) Pre-operative imaging demonstrates a large tuberculum sellae/posterior planum meningioma with extension into the sella. Bilateral optic canal invasion is seen, right more than left (red arrow). There is no supraclinoid carotid artery encasement, or lateral extension. The pituitary infundibulum is displaced posteriorly. An endoscopic transtuberculum/transplanum approach was performed. (Bottom row) Post-operative imaging shows gross total resection. Sagittal CT and MRI demonstrates nasal packing up ("M") to the bony buttress (posterior nasal septum graft; blue arrow) with fat graft and collagen sponge in the resection cavity and a well-vascularized nasoseptal flap is in place with pituitary gland and infundibulum enhancing normal. Within 2 weeks of surgery her visual field deficit resolved, and visual acuity remained stable. See Video 1.

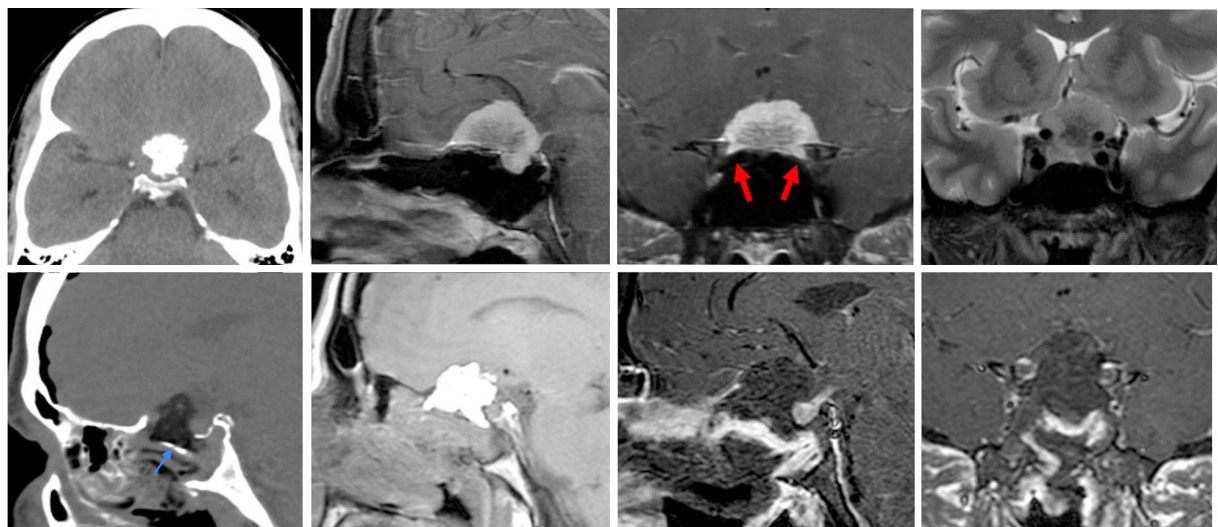


Figure 3. A 39-year-old man presented with progressive left eye vision loss over several months. Pre-operative imaging demonstrates a large, calcified tuberculum sellae/planum meningioma with extension into the sella. Bilateral optic canal invasion is seen, left more than right (red arrows). The left internal carotid artery is encased, with significant encroachment upon the right carotid artery. An endoscopic transtuberculum/transplanum approach was performed without complication. Post-operative MRI demonstrates gross total resection. A fat graft is in the resection cavity with a well-vascularized nasoseptal flap over a bony buttress (posterior nasal septum graft; blue arrow). The pituitary gland and infundibulum enhance normally.

Bone removal

Once the sphenoid sinus has been entered, any bony septations are carefully removed using a rongeur or high-speed drill with a 4 mm course diamond bit. Special attention is paid to lateral septations as they often lead directly to the petrous and cavernous carotid arteries. Aggressive removal or torquing of these septations is avoided as such maneuvers can result in carotid artery laceration. At this stage, several important landmarks should be identified using the 30° endoscope, including the optic and carotid prominences, lateral opticocarotid recess (OCR; corresponding to the optic strut), medial OCR (delineating

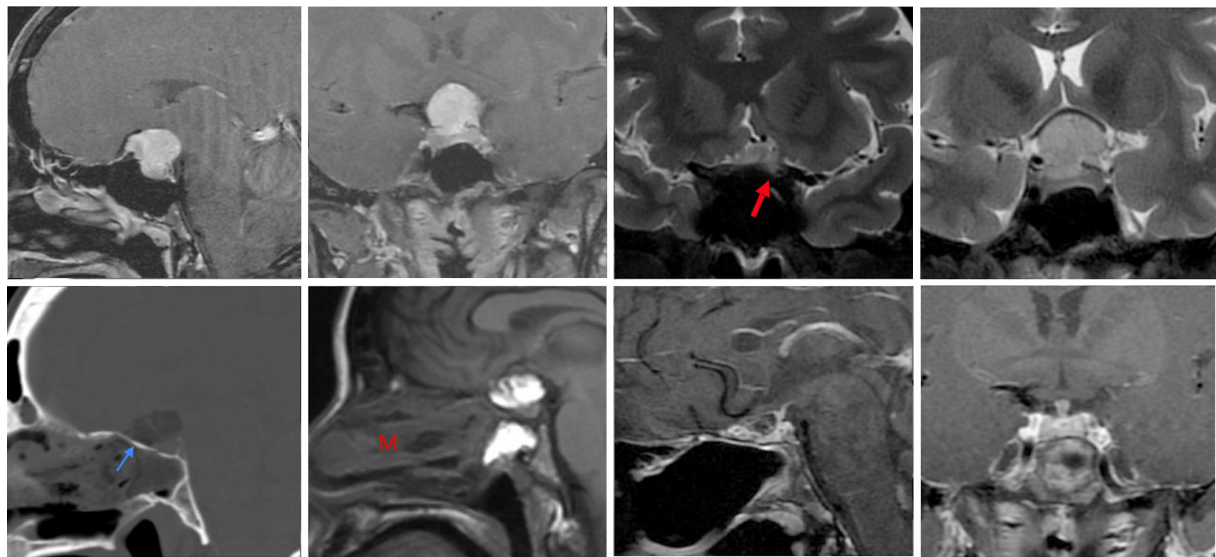


Figure 4. A 46-year-old woman presented with severe left eye vision loss and progressively worsening right eye vision, with a right inferior field cut. She also had amenorrhea with mild hyperprolactinemia, presumably from stalk effect. Pre-operative imaging demonstrates a large tuberculum sellae meningioma with a severely displaced optic apparatus and left optic canal invasion (red arrow), but no arterial encasement or lateral extension beyond the supraclinoid ICAs. The pituitary infundibulum is displaced posteriorly. An endoscopic transtuberculum approach was performed with a gross total resection achieved. A sellar fat graft and well-vascularized nasoseptal flap is seen overlying a bony buttress (posterior nasal septum graft; blue arrow) reinforced with nasal packing (“M”). The pituitary gland and infundibulum enhance normally. The patient demonstrated marked improvement in visual acuity and visual fields and her menses returned with normalization of serum prolactin.

the lateral aspect of the sella), clival recess, tuberculum sellae and planum sphenoidale. These structures should be verified with neuronavigation and the micro-Doppler probe used to identify the ICAs. The bone of the sellar face, tuberculum sellae and the planum sphenoidale is then thinned with the drill to expose the dura. Kerrison rongeurs are used to remove the thinned bone. The sagittal extent of exposure depends on the size of the meningioma and should extend from the sella (but leaving an inferior lip or shelf of sellar bone to aid in reconstruction) to just beyond the anterior edge of the tumor on the posterior planum. The coronal exposure should be from medial OCR to medial OCR, with wide exposure of the planum sphenoidale. If there is extension into one or both optic canals, these should be unroofed. A 3 mm hybrid diamond bit with irrigating sheath is used and then once the proximal canal bone is “egg-shelled”, it is further opened with a 1 mm Kerrison rongeur working in the proximal-to-distal direction.

Dural opening

Prior to dural opening, the location of the ICAs is precisely determined with a micro-Doppler probe and surgical navigation. Next, the dural “footprint” of the tumor from just above the diaphragma sellae to its anterior extend on the posterior planum is lightly cauterized with the bipolar for initial tumor devascularization. The dura is then opened in rectangular fashion over the tumor epicenter with horizontal dural cuts made along the top of the pituitary gland and just below the circular sinus (which is cauterized and cut) and at the anterior tumor edge. The lateral dural cuts are then made and connected with the supradiaphragmatic incision, and the dural window is removed.

Tumor removal

The meningioma is then internally debulked, typically with sharp dissection using microscissors, tumor grasping forceps and the ultrasonic aspirator. Most meningiomas are too fibrous for use of ring curettes. We generally begin mobilizing the tumor capsule from the adjacent arachnoid anteriorly as there are generally

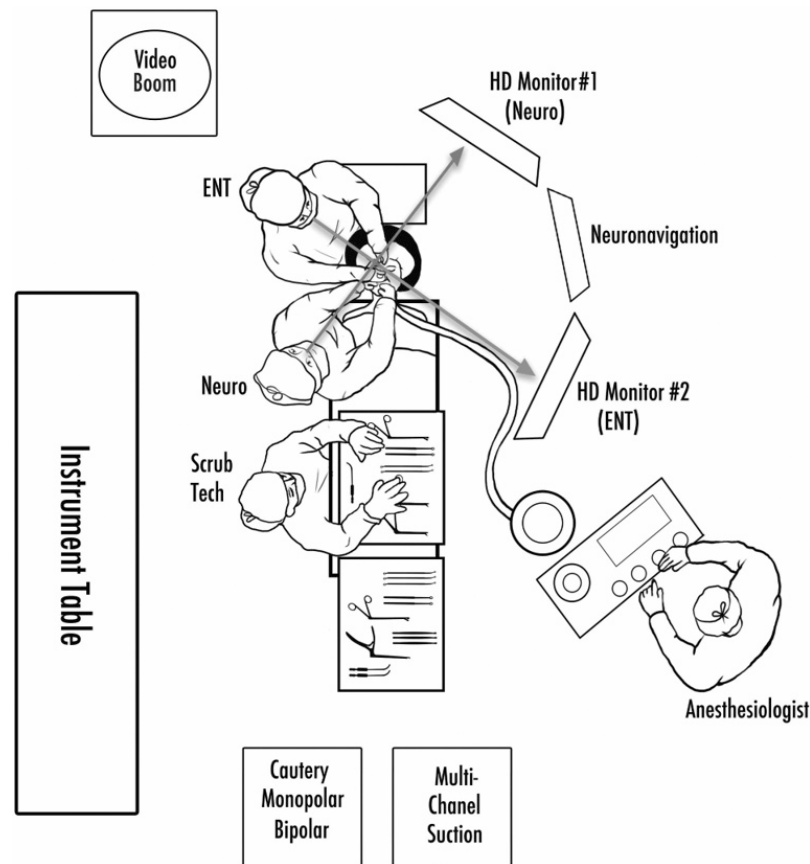


Figure 5. Diagram of the operating room setup for endoscopic endonasal surgery. The procedure involves an otolaryngologist and neurosurgeon, both positioned on the patient's right side. Ergonomics are optimized by having an endoscope monitor positioned directly in front of each surgeon as well as an arm rest for the otolaryngologist's left arm, holding the endoscope.

no critical structures in this location. Using sharp dissection and preserving the arachnoid planes, the tumor capsule is methodically dissected away from the overlying frontal lobe. After the initial tumor debulking, it is also helpful to identify the superior surface of the pituitary gland and infundibulum to avoid injuring these structures. To achieve this view, the inferior pole of the tumor, which is often attached to the diaphragma sellae, is detached and progressively removed. The infundibulum will lie posterior and inferior to the tumor. The paired superior hypophyseal arteries and their branches going to the optic chiasm are also preserved. Subsequently, the tumor pseudocapsule is gently pulled inward and arachnoid bands between the tumor, optic apparatus and the superior hypophyseal arteries are cut sharply. The optic chiasm may be markedly post-fixed (pushed posteriorly) or lifted superiorly and posteriorly. Progressive internal tumor debulking will allow the optic chiasm and optic nerves to be progressively visualized. With further medial mobilization and removal of the most lateral tumor capsule, the distal optic nerves will become visualized. Frequent removal of freed tumor capsule is paramount to maintain optimal visualization of the optic apparatus. The anterior cerebral arteries and branches should be anticipated, and their shifting location confirmed frequently with the micro-Doppler probe as the tumor debulking progresses, given that neuronavigation becomes less accurate after initial tumor removal and brain shift. If anterior cerebral artery (ACA) branches or the supraclinoid ICA itself is partially encased by meningioma, it is often best to leave small tumor remnants behind to avoid a major vascular injury and stroke, particularly in older patients and those with cardiovascular disease.

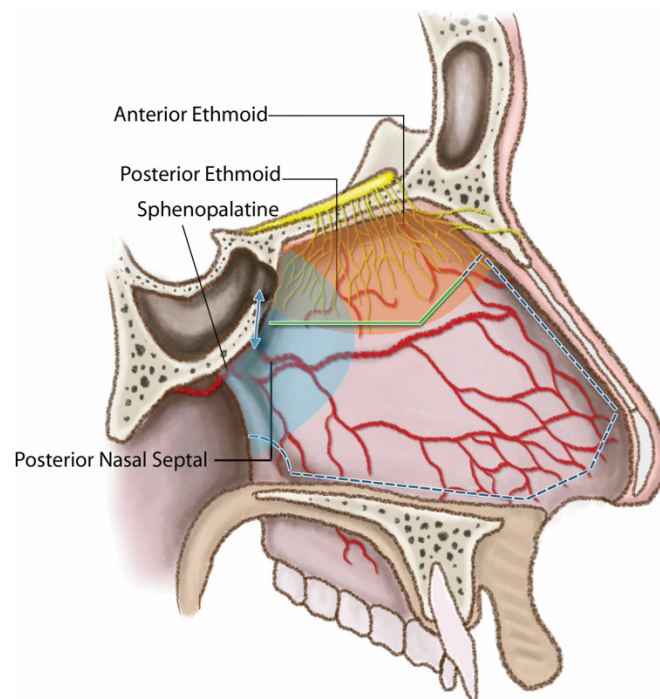


Figure 6. Lateral view of the nasal septum depicting the mucosal cut made for elevating a nasoseptal flap (dashed line) during an endoscopic transtuberculum/transplanum approach, preserving olfaction by sparing the septal olfactory strip above which contains the olfactory nerve fibers. A rescue flap incision (solid line) is made on the other side, again aimed at preserving olfaction.

If there is meningioma growth into one or both optic canals, this tumor may be addressed once the majority of the tumor has been resected. The bone of the medial aspect of the optic canal should be decompressed as described above. Then, using a hook knife, the optic nerve sheath can be opened from medial to lateral once the ophthalmic artery takeoff has been visualized infero-medially. A 45° endoscope may be helpful at this stage to clearly visualize and achieve maximal tumor removal within the medial optic canals.

Skull base reconstruction

Once tumor removal is complete, the resection cavity is irrigated with warm saline and hemostasis is achieved. By definition, a high flow, Grade 3 CSF leak will be present due to dural resection^[31]. Sufficient abdominal fat is harvested to fill the intracranial dead space, taking care not to recreate too much mass effect on the optic apparatus. The fat is followed by an extradural layer of collagen sponge extending only 1-2 mm beyond the bony edges of the surgical corridor; this placement allows maximal contact of the nasoseptal flap with the bone around the defect. Ideally, harvested septal bone (or alternatively a synthetic buttress) is carefully wedged from the inferior sellar lip to the antero-superior defect within the bony defect. The nasoseptal flap is then rolled over the bony skull base defect with care being taken to ensure there is no redundancy or folds in the flap. The flap should fully cover the defect and extend beyond its edges as far as possible with maximal contact on the bone adjacent to the defect. Additional fat is placed over the flap followed by an outer layer of collagen sponge and tissue glue. An additional layer of collagen sponge is placed over the fat graft and then reinforced with unilateral or bilateral Merocel (Medtronic, Dublin, Ireland) sponges placed under direct visualization. The patient remains on antibiotics for the 5 days while the Merocel sponges remain in place and then are removed under direct visualization. While the optimal duration of nasal packing is debated, based on our experience, 5 days appears to be sufficient to ensure adherence of the reconstruction to the skull base^[31]. We have experienced no instances of sinonasal infection. A nasogastric tube is briefly placed to empty the stomach contents to minimize the risk of post-

operative emesis. Similarly, total intravenous anesthesia with propofol is used with a smooth emergence from anesthesia to avoid post-operative emesis and “bucking” on the endotracheal tube during extubation^[32]. In our experience, lumbar drainage is not necessary to ensure effective reconstruction^[31].

Should a nasoseptal flap not be available, other vascularized flaps may be considered such as a pedicled middle or inferior turbinate flap or pericranial flap tunneled through a nasionectomy^[33,34]. In cases with no available vascularized options, multilayered avascular reconstructions with autologous fat, fascia lata and synthetic materials reinforced with Merocel (Medtronic, Dublin, Ireland) sponges may be required, although CSF leak rates tend to be higher compared to vascularized reconstruction techniques^[35].

An important aspect of skull base reconstruction to be stressed is to utilize a protocol based on the degree of intra-operative CSF leak. Planning the reconstruction, including back-up options, prior to surgery and adjusting as necessary based on intra-operative findings will help ensure a low post-operative CSF leak rate of less than 5% and hopefully much lower, even for high-grade leaks encountered in anterior cranial fossa surgery^[31].

Outcomes

Recent series have indicated overall excellent visual outcomes for tuberculum sellae meningiomas approached by the endonasal route [Table 1]^[13,24,26,36-43]. Yang *et al.*^[19] performed a meta-analysis of studies assessing the endonasal endoscopic route *vs.* transcranial approaches for tuberculum sellae meningiomas and found higher rates of visual improvement (85.7% *vs.* 55.1%) in the endoscopic cohort with similar rates of gross total resection (74.5% *vs.* 76.1%). CSF leak rates were significantly higher in the endoscopic cohorts (8.6% *vs.* 2.1%), although we have recently published a CSF leak grading scale and recommended skull base reconstruction protocol that has resulted in a CSF leak rate of only 2% (1 of 49 patients) of patients with high flow (Grade 3) CSF leaks^[31]. A recent meta-analysis has demonstrated a significant decrease in CSF leak rate over time to 4% with the endoscopic endonasal approach, reported in the last 5 years^[44].

In 2020, Youngerman *et al.*^[45] published a resectability scoring system to predict gross total resection for planum sphenoidale and tuberculum sellae meningiomas using the endoscopic endonasal route. One point is assigned to each of the following: (1) prior surgery; (2) complete ICA encasement on more than 1 MRI plane; and (3) lateral extension of the tumor beyond the lateral margin of either optic nerve. Using their case series of 51 operations, they found that scores of 0, 1 and 2 were associated with gross total resection rates of 97%, 54% and 12.5%, respectively. They found that tumor size, medial optic canal involvement, brain edema and encasement of the anterior cerebral arteries were not predictive of gross total resection.

Complications

While endoscopic endonasal surgery places the tuberculum sellae/planum sphenoidale meningioma in direct line of site, the surrounding critical structures may be at risk of iatrogenic injury as the tumor may be quite adherent to these structures or encase them. Thorough pre-operative planning, in addition to the diligent use of neuronavigation and micro-Doppler probe, is highly recommended to minimize risks of complications. Injury to the ICA and ACA should be immediately investigated to find the bleeding site with an attempt to repair with clip ligation, tamponade with muscle tissue or synthetic material, or sacrifice of the parent vessel as deemed necessary. Once the bleeding has been stabilized, the procedure should be aborted, and the patient is brought to the angiography suite for evaluation and treatment of arterial injury and/or pseudoaneurysm formation. At our institution, we have implemented a “carotid injury timeout” in conjunction with a standard operative timeout for high-risk procedures. Additional equipment is made available in the room to deal with a major arterial injury, including essential instruments, backup equipment, medications and crossmatched blood. The neuro-interventional team is notified prior to the

Table 1. Demographics and outcomes for recent case series of endoscopic transsphenoidal/transplanum approach for tuberculum and posterior planum meningiomas

Ref.	Year	N	Female (%)	Arterial encasement (%)	OC invasion (%)	Vision symptoms (%)	Post-op vision improvement (%)	GTR (%)	Complications (%)	Recurrence (%)
Khan et al. ^[42]	2014	17	76	NR	NR	82	64	65	CSF leak: 12 Hypopituitarism: 6	NR
Koutourousiou et al. ^[13]	2014	75	81	25	27	81	79	76	CSF leak: 25 Meningitis: 5 Vision loss: 4 Stroke: 1	5
Ottenhausen et al. ^[36]	2014	20	70	NR	NR	85	82	80	CSF leak: 10 Infection: 5 PE: 5	10
Hayhurst et al. ^[43]	2016	10	70	NR	80	40	0	60	CSF leak: 0	NR
Linsler et al. ^[41]	2017	6	100	16	NR	50	67	83	CSF leak: 0	16
Bander et al. ^[26]	2018	17	65	NR	NR	88	67	82	CSF leak: 12	NR
Elshazly et al. ^[38]	2018	25	84	ACA: 12 ICA: 32	68	80	88	76	CSF leak: 8 Hematoma: 4 PE: 4	0
Kong et al. ^[24]	2018	84	76	NR	94	95	85	83	CSF leak: 5 Meningitis: 7 Vision loss: 5	NR
Song et al. ^[37]	2018	44	NR	25	77	100	98	84	CSF leak: 0 Meningitis: 3 Vision loss: 36 ICA injury: 3 Permanent DI: 3 Hypopituitarism: 5 Hematoma: 5	15
Zoli et al. ^[39]	2018	42	NR	NR	NR	VA: 67 VF: 57	VA: 68 VF: 75	83	CSF leak: 19 Stroke: 2	5
Salek et al. ^[40]	2020	8	63	13	50	100	88	75	CSF leak: 25	13

ACA: Anterior cerebral artery; CSF: cerebrospinal fluid; DI: diabetes insipidus; GTR: gross total resection; ICA: internal cerebral artery; N: number; NR: not reported; OC: optic canal; PE: pulmonary embolism; VA: visual acuity; VF: visual field.

operation.

Meticulous dissection of the optic nerves and chiasm, including careful preservation of small perforators to the optic apparatus, including the superior hypophyseal arteries, is required to prevent post-operative vision decline. Endoscopic endonasal series have reported worsening vision in up to 36%, with more recent series reporting much lower rates of less than 5% [Table 1]^[11,13,23,24,26,36-43,45-51]. CSF leaks from this approach are high flow (Grade 3 leaks) requiring a robust reconstruction, ideally with a nasoseptal flap. As outlined above, we have recently published our skull base reconstruction protocol which has resulted in a CSF leak rate of 2% for high flow (Grade 3) leaks^[31].

Other complications include permanent post-operative anterior endocrinopathy or diabetes insipidus (6.6%), intracranial hemorrhage (0.7%) and dysosmia (21.9%)^[19]. Importantly, we utilize a nasoseptal flap harvest technique that preserves the septal olfactory strips located in the superior portion of the nasal septum, thus preserving olfaction in greater than 97% of patients^[52].

TRANSCRIBRIFORM APPROACH TO PLANUM & OLFACTORY GROOVE MENINGIOMAS

Patient selection & surgical considerations

The endoscopic endonasal transcribriform approach is an effective way to approach olfactory groove meningiomas as it provides direct access to the anterior cranial fossa floor dura and the feeding arteries. Other advantages over traditional transcranial trajectories include lack of brain retraction, increased possibility of Simpson grade 1 resection and excellent visualization of surrounding critical structures. However, loss of olfaction is virtually guaranteed in this approach due to disruption of the olfactory fibers traversing the cribriform plate. Furthermore, the anatomical limitations are well defined, restricting the use of this approach to a subset of patients with smaller olfactory meningiomas. The orbits limit access laterally, although the lamina papyracea can be removed and gentle displacement of the periorbita provides access to the midorbital sagittal plane. Tumor involvement superiorly along the posterior wall of the frontal sinus becomes increasingly difficult to visualize and reach. Careful patient selection with thorough evaluation of MRI and CT imaging is required when using this approach to maximize success.

At our center we utilize a supraorbital craniotomy for the great majority of olfactory groove meningiomas as it allows olfaction to be preserved in most cases, with laterality determined by the side with more olfactory nerve involvement to preserve the unaffected olfactory nerve. This approach requires minimal-to-no brain retraction, and endoscopes with angled instruments are used in patients with a deep olfactory groove to remove tumor not visualized with the microscope [Figure 7].

Surgical technique

Patient positioning, approach and bony exposure

The patient is positioned with the head in slight extension similar to the transplanum/transtuberculum approach. The same nasal phase proceeds with harvesting a nasoseptal flap, sphenoidotomy and bilateral ethmoidectomies. One of the middle turbinates is often removed to fully expose the fovea ethmoidalis on either side. Bilateral mastoid antrostomies may be performed to aid in identification of each lamina papyracea. With the use of a 30° endoscope, mucosa is removed from the superior aspect of the nasal septum and the anterior skull base, and a superior septectomy is performed. With the cribriform plate exposed, the lateral boundaries with the laminae papyraceae are identified, as well as the posterior boundary with the planum sphenoidale. The anterior border with the posterior table of the frontal sinus is identified through the completion of a Draf III procedure with removal of the frontal sinus floor and inferior portion of the interfrontal septum. A prominent frontal beak may need to be removed.

After completely exposing the cribriform plate and each fovea ethmoidalis, the bone is thinned down with a drill. The bony prominences overlying the anterior and posterior ethmoid arteries are identified, carefully thinned and removed. The arteries are then coagulated and divided to avoid an orbital hematoma. A craniectomy is then completed with the drill and Kerrison rongeurs, the boundaries of which are determined by the access required for the meningioma and dural tail. Hyperostotic bone is removed. If removal of the crista galli is required, it is carefully dissected from the falx cerebri.

Tumor removal and skull base reconstruction

Exposed dura of the anterior cranial fossa is thoroughly coagulated to disrupt blood flow to the meningioma. Lateral incisions are made on each side, followed by an anterior incision with transection of the falx. It is important to cut the falx in a posteroinferior direction to avoid injuring the superior sagittal sinus. An emissary vein through the foramen cecum may be encountered. Finally, a posterior incision is made. Similar to removal of tuberculum sella meningiomas, the tumor is then internally debulked and the capsule gently dissected from the surrounding orbitofrontal cortex using standard microsurgical techniques.

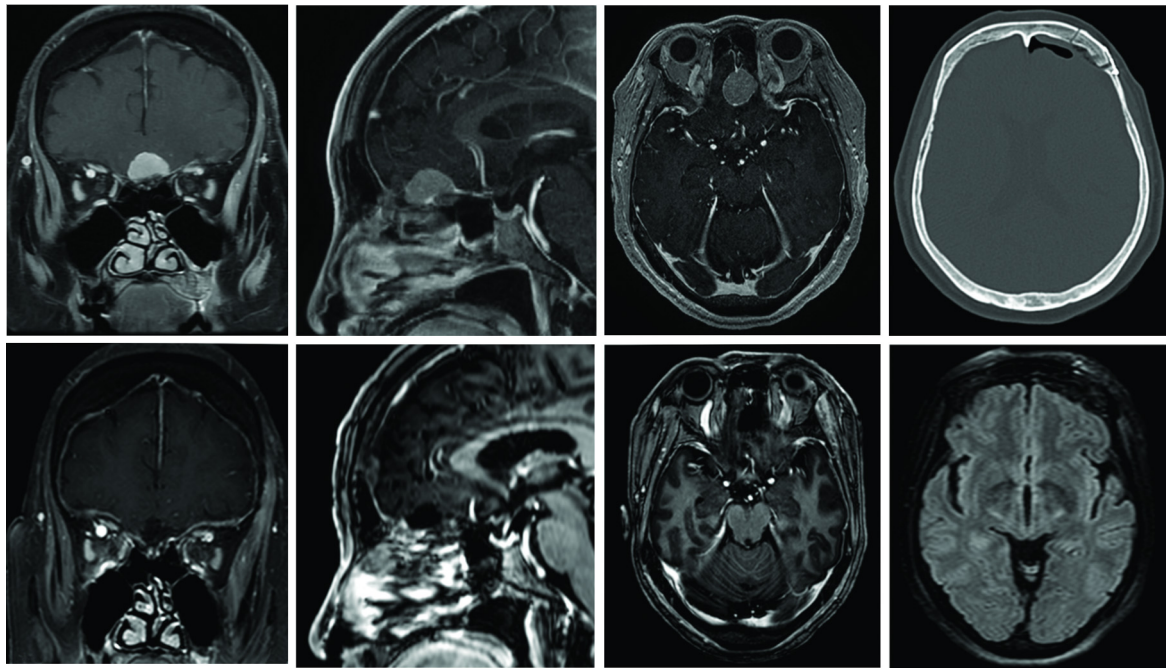


Figure 7. A 68-year-old female presented with progressive periorbital headaches with preserved olfaction. (Top Row) Pre-operative imaging demonstrates an olfactory groove meningioma extending posteriorly to the anterior portion of the planum sphenoidale. The lateral extent of the tumor is confined within the medial aspects of the orbits bilaterally. This tumor is therefore amenable to an endoscopic endonasal transcribriform approach, however, to preserve olfaction we elected to approach this tumor through a left supraorbital eyebrow craniotomy. (Bottom Row) Post-operative imaging demonstrates gross total removal of the meningioma. Top right image shows a post-operative CT scan demonstrating the size of the supraorbital craniotomy. The endoscopic was used to ensure removal of tumor within the depths of the olfactory groove. Axial FLAIR imaging demonstrates no retraction injury to the left frontal lobe. Olfaction was preserved. An endoscopic endonasal transcribriform approach would have guaranteed loss of olfaction and therefore is not the optimal approach.

If there is encasement of the ACAs, early identification posteriorly provides proximal control, and as with tuberculum sellae meningiomas, frequent use of the micro-Doppler probe to map the course of these shifting arteries is recommended.

Effective skull base reconstruction is required due to the inevitable Grade 3 CSF leak and large skull base defect. This reconstruction is performed similarly to the transplanum/transtuberculum approach with a multilayered closure involving a fat graft to fill the dead space, collagen sponge, nasoseptal flap, solid bony or synthetic buttress and tissue glue. A lumbar drain is not used in our practice^[31].

Outcomes

A recent systematic review found that gross total resection of olfactory groove meningiomas through an endoscopic endonasal transcribriform approach was achieved in 69.5% of patients^[53]. Comparison studies have consistently reported higher rates of gross total resection with traditional transcranial approaches at approximately 93%^[21,42,43,54-61]. While surgeon experience with the transcribriform approach leads to increased rates of gross total resection, tumor size (greater than 4 cm), lateral extension beyond the midorbital line, tumor calcifications, significant brain edema and neurovascular encasement limit success. Olfactory groove meningiomas that extend posterior to the optic apparatus may cause visual symptoms, particularly when optic canal invasion is present. In a recent systematic review by Shetty *et al.*^[18], 80.7% of patients with vision symptoms experienced an improvement after endoscopic endonasal surgery, compared to 12.8% of transcranial approaches. No vision deterioration was reported in the endonasal cohort. Similar to

tuberculum sellae/planum sphenoidale meningiomas, transcranial approaches are limited in their ability to visualize the inferomedial portion of the ipsilateral optic canal, where tumor invasion generally occurs. Thus, we hypothesize that this discrepancy may be related to excessive manipulation of the optic apparatus and/or insufficient decompression of tumor within the optic canal from above. An endonasal approach provides direct access to the medial 180° of the optic canals, enabling the opportunity for effective decompression and tumor removal. A summary of recent case series is presented in [Table 2](#)^[39,42,43,55-57,62].

As mentioned previously, loss of olfaction (if not present pre-operatively) is virtually guaranteed with the transcribriform approach due to disruption of the olfactory fibers. This sensory loss has been shown to have a significant impact on quality of life^[52,63]. While a unilateral transcribriform approach has been described to preserve contralateral olfaction, the indications for this technique are highly specific and thus not applicable to the vast majority of patients with olfactory groove meningiomas^[64].

Complications

Aside from loss of olfaction, CSF leak and meningitis are the most common complications. While the rate has decreased with the use of nasoseptal flaps, it remains a challenge for large olfactory groove meningiomas with rates of 26% to 30% in the largest series^[54,57]. Regarding most transcranial approaches for olfactory groove meningiomas, CSF leak rates have ranged from 8.4% to 10%, while we have recently reported a 1% CSF leak rate with the supraorbital craniotomy approach^[10,58]. Other complications reported by Koutourousiou *et al.*^[57] include hydrocephalus in 6%, new onset seizures in 4%, meningitis in 2%, cerebral abscess in 6%, and deep venous thrombosis/pulmonary embolism in 20%. A high complication rate is thought to be attributed to the long operative time required for this approach.

CONCLUSION

Endoscopic endonasal approaches to anterior skull base meningiomas have evolved substantially and are commonly used today at many centers. While the indications are still debated, several advantages exist for the endoscopic route over traditional transcranial approaches, including the ability to remove hyperostotic bone, obtaining direct access to the dura and feeding arteries, minimal brain manipulation, excellent visualization with the endoscope, displacement of critical surrounding structures away from the surgical corridor, and improved vision outcomes with medial optic canal decompression. In our experience and that of others, a majority of tuberculum sellae and posterior planum meningiomas can be safely and effectively removed through an endoscopic endonasal approach, although requisite experience, instrumentation and careful selection of appropriate cases is essential to success. In contrast, a minority of olfactory groove meningiomas are ideally approached from an endonasal route, particularly for those in whom olfaction is already absent, and they do not extend too far laterally. Otherwise, a transcranial route may be most appropriate.

Careful patient selection is paramount to success in removing these anterior skull base meningiomas as there are several important anatomic limitations of the transnasal corridors that must be identified. With modern skull base reconstruction techniques, CSF leak rates are low, particularly for the transplanum/transtuberculum approach. Utilizing endoscopic endonasal routes alongside minimally invasive transcranial approaches, such as the supraorbital keyhole craniotomy, meningiomas of the anterior skull base may be treated effectively with excellent oncological, functional and cosmetic outcomes. Thus, both the endoscopic endonasal and endoscope-assisted supraorbital route should be considered part of the modern surgical armamentarium for these challenging skull base meningiomas.

Table 2. Demographics and outcomes for recent case series of endoscopic transcribriform approach for olfactory groove meningiomas

Ref.	Year	N	Female (%)	Arterial encasement (%)	Vision symptoms (%)	Post-op vision improvement (%)	GTR (%)	Complications (%)	Recurrence (%)
Khan et al. ^[42]	2014	6	100	NR	33	100	50	CSF leak: 33	0
Koutourousiou et al. ^[57]	2014	50	64	NR	30	87	67	CSF leak: 30 PE/DVT: 20 Infection: 10 Vascular injury: 2	2
de Almeida et al. ^[56]	2015	10	70	10	NR	NR	70	CSF leak: 10 Meningitis: 10 MI: 10	10
Banu et al. ^[55]	2016	6	100	0	17	100	50	CSF leak: 17 Infection: 33 Hematoma: 33 Stroke: 17 PE/DVT: 17	33
Hayhurst et al. ^[43]	2016	9	89	NR	NR	NR	89	CSF leak: 0 Meningitis: 11	NR
Liu et al. ^[62]	2018	5	80	0	NR	NR	100	CSF leak: 20 Hematoma: 20	20
Zoli et al. ^[39]	2018	8	NR	NR	NR	NR	63	CSF leak: 13	25

CSF: Cerebrospinal fluid; GTR: gross total resection; MI: myocardial infarction; N: number; NR: not reported; PE/DVT: pulmonary embolism/deep venous thrombosis.

DECLARATIONS

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Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Avery MB, Barkhoudarian G, Kelly DF

Performed data acquisition, as well as provided administrative, technical, and material support: Avery MB, Barkhoudarian G, Kelly DF

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Kelly DF receives royalties from Mizuho Inc.

Barkhoudarian G is a consultant for Vascular Technologies Inc.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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The current status of watchful waiting for inguinal hernia management: a review of clinical evidence

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Abstract

Inguinal hernias are a very common problem and the most common reason for primary care physicians to refer patients for surgery. The diagnosis is usually made from history and physical examination and men are significantly more likely to be affected than women. Most patients will present with a painful bulge in the groin, though up to a third of patients will be asymptomatic at the time of diagnosis. Previously, it had been recommended that all hernias be repaired surgically at the time of diagnosis to prevent the development of a hernia accident (bowel obstruction or strangulation) that would require emergent surgery, which is associated with much higher morbidity and mortality than an elective repair. However, several clinical trials have reported that risks of a hernia accident are sufficiently low so that a “watchful waiting” (WW) approach for male patients who are asymptomatic or minimally symptomatic is a safe management strategy. WW spares patients any risk of operative complications related to their herniorrhaphy, perhaps the most significant of which is post-herniorrhaphy groin pain that has only recently been appreciated as a significant issue. Although WW has now been proven to be safe in asymptomatic males with an inguinal hernia, long-term results of randomized controlled trials have shown that most patients initially managed with WW will eventually elect to have the hernia surgically repaired primarily due to increased pain. The purpose of this article is to review the current evidence on watchful waiting for the management of inguinal hernias.

Keywords: Inguinal hernia, watchful waiting, groin hernia, herniorrhaphy



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INTRODUCTION

Groin hernias are a very common problem with presentation ranging from patients who are completely asymptomatic to those with the life-threatening complication of strangulation or bowel obstruction, referred to as a hernia accident. Over 1.6 million hernias are diagnosed each year in the United States alone, of which 500,000 are surgically repaired^[1]. Of the groin hernias in the United States, 96% are classified as inguinal hernias and 4% are femoral^[2]. Men are significantly more likely to develop a groin hernia than women; the lifetime risk of is 27% for men and 3% for women^[1]. Two-thirds of patients will present with a painful bulge in the groin and diagnosis is made primarily through history and physical examination with imaging rarely required^[3]. Up to one third of inguinal hernia patients present asymptotically without pain or other factors that lead to impairment of daily functioning^[4].

Management of inguinal hernias has evolved over time to improve quality of life and limit safety risk to the patient. Historically, it was recommended that all patients presenting with an inguinal hernia have it repaired surgically at the time of diagnosis due to the prevailing belief that the risk of a hernia accident (bowel obstruction and/or strangulation) was significantly high enough to contraindicate watchful waiting (WW). However, more recent evidence of WW has emerged that has shown that WW is a safe and acceptable alternative to surgical repair for asymptomatic or minimally symptomatic inguinal hernia patients. Avoiding operative repair in asymptomatic patients through a WW approach precludes any potential development of pain related to the operation as well as the other standard risks associated with major surgery (e.g., hemorrhage, infection, and recurrence). Post-herniorrhaphy groin pain has now come to the forefront of issues facing groin hernia surgeons as some studies suggest that as many as 15% of patients experience post-herniorrhaphy inguinal groin pain that affects their daily lives 6 months after the operation^[5].

To date, three major clinical trials from North America, the United Kingdom and the Netherlands have investigated outcomes after randomization of patients presenting with asymptomatic or minimally symptomatic inguinal hernias to a WW approach vs. routine elective surgical repair^[6-8]. While all completed trials support WW as a viable and safe approach for some patients in the initial treatment of inguinal hernia management, long-term follow-up has found that most (approximately 70%) of patients who elect to forego hernia repair will eventually be treated surgically due to worsening pain or lifestyle limitations from progression of symptoms. The purpose of this article is to provide an overview of the current status of watchful waiting as an option for initial inguinal hernia management and review the clinical evidence from randomized controlled trials that led to the adaptation of WW as an acceptable alternative to an operative approach.

WATCHFUL WAITING

The risks and benefits of WW as an approach for inguinal hernia management in patients who are asymptomatic or mildly symptomatic were investigated in three randomized controlled trials from North America, the UK, and the Netherlands. Asymptomatic or minimally symptomatic patients were defined as those patients whose hernia-related discomfort did not limit activities of daily living and who did not exhibit difficulty in manually reducing the hernia^[6]. An important distinction is necessary to recognize in the optimal management of hernias between men and women. Currently, the approach of WW is only an appropriate strategy for men because women are significantly more likely to develop femoral hernias, which are more prone to strangulation^[9]. It is difficult to distinguish inguinal hernias from femoral hernias, so surgical repair is recommended for all nonpregnant women with groin hernias^[10]. Pregnant women with a groin bulge which appears to be a hernia should be imaged with ultrasound to rule out round ligament varicosities, a common cause of a groin bulge in a pregnant female, before surgery is considered^[10].

NORTH AMERICAN TRIAL

A randomized control trial with 720 men, 18 years of age or older with inguinal hernias who presented asymptotically or with minimal symptoms was completed in North America in 2006, showing WW as a safe alternative to surgical repair^[6]. Patients were assigned to either a WW or a Lichtenstein repair approach and followed to observe differences in development of a hernia accident between the two groups. Patients were similar at baseline in terms of age, American Society of Anesthesiology classification, preexisting conditions, hernia type, and hernia characteristics. At 2 years of follow-up, only 1 patient (0.3%) required emergent surgery for an acute hernia incarceration and the patient was not found to have strangulation. There was no difference in quality of life between the two groups at 2 years. Patients in the WW group crossed over to the surgical repair group at a rate of 23%, most commonly due to pain, and were more likely to do so if they had reported higher levels of pain at the start of the trial. At 4.5 years of follow-up, only one additional patient in the WW group developed acute incarceration with bowel obstruction, for a total surgical emergency rate of 1.8 per 1000 person-years at the end of the trial. Although this study clearly showed that WW was a safe alternative to routine repair for minimally symptomatic males, subsequent long-term follow-up at 10 years showed that 68% of patients originally in the WW group had crossed over to surgical repair, mostly due to increased pain^[11]. The authors recommended that men with minimally symptomatic inguinal hernias be informed that WW is a safe preliminary management choice to avoid immediate operative intervention but most individuals will eventually undergo surgical repair if they live long enough.

UNITED KINGDOM TRIAL

In this trial, 160 men aged 55 years or older with minimally symptomatic inguinal hernias were enrolled in a single-center randomized controlled trial to investigate WW vs. surgical repair^[7]. At one year of follow-up, there were no significant differences in pain scores between the watchful waiting and surgical repair cohorts, although the surgical repair group did report improvement in their perceived quality of life. The crossover rate from WW to surgery was 29% at one year, with increasing pain and enlargement of the hernia responsible for most cases of crossover. The incidence of serious events in the WW group was minimal; one patient developed a hernia incarceration and two others experienced cardiovascular events after crossover to the repair group. The authors hypothesized that the cardiovascular complications could have been prevented had the patients undergone surgical repair at the start of the trial, but this has been criticized by other authorities as highly speculative^[12]. Similar to the North American Trial, long-term follow-up disclosed a high crossover rate to surgery (72% at 7.5 years by Kaplan-Meier analysis), demonstrating that for most patients who present with an inguinal hernia, surgical repair will eventually become necessary^[13].

NETHERLANDS TRIAL

In 2018, researchers in the Netherlands reported results from a multicenter randomized controlled trial to determine the noninferiority of WW compared to elective hernia repair in 496 men aged 50 years or older who presented with mildly symptomatic or asymptomatic inguinal hernias^[8]. The primary outcome measure was pain and discomfort at 2 years of follow-up using a 4-point pain/discomfort score which ranged from no pain or discomfort to severe pain or discomfort due to the hernia while working, exercising or performing any of a patient's usual activities. Secondary endpoints included: health-related quality of life as measured by the Short-Form 36 (SF-36) questionnaire, overall 3-year crossover rate in patients assigned to watchful waiting, 3-year event-free survival between the 2 treatment groups, hernia complication (incarceration or strangulation), ischemic orchitis, and recurrent hernia. The EuroQol-5D (EQ-5D) questionnaire was also assessed at baseline, 3, 12, 24, and 36 months. The EQ-5D included a visual analog scale (VAS) to rate overall health status on a scale of 0 (worst imaginable health state) to 100 (best

imaginable health state). The patient pain/discomfort score was found to be 0.35 [95% confidence interval (CI): 0.28-0.41] in the elective repair group and 0.58 (95%CI: 0.52-0.64) in the WW group. The difference of these means (MD) was - 0.23 (95%CI: 0.32-0.14), showing that a relevant difference in favor of elective repair could not be ruled out. Ninety-nine patients (37.8%) crossed over from the WW cohort to surgical repair, mostly due to worsening pain. Six patients (2.3%) underwent emergent surgery for strangulation or incarceration but none suffered adverse sequelae such as the need for bowel resection after three years of follow-up. The 3-year event-free survival was 80.9% in the surgical repair group and 77.2% in the WW group. The cumulative incidence of patients with at least one or more events (recurrence, moderate to severe pain, ischemic orchitis, hernia complications, etc.) in the surgery repair and WW groups was 17.5% and 20.6%, respectively at three years. Although a statistically significant advantage for WW over routine repair was not demonstrated, the authors concluded that when looking at the primary and secondary endpoints as a whole, watchful waiting was a reasonable alternative compared with routine elective surgery in male patients. Due to the recency of the trial's completion, long-term analysis is not yet available.

SIMILARITIES BETWEEN TRIALS

Generally, all three trials reached the same conclusion: WW is a safe and appropriate strategy for initial management of inguinal hernia in male patients who present with minimal or no symptoms. The previous belief held by many surgeons that a significant proportion of patients not treated by surgical repair upon presentation would suffer a hernia accident which would result in a significant increase in morbidity and mortality was not supported. Few patients in the WW cohorts exhibited serious hernia accidents in short- and long-term follow-up. Table 1 describes notable findings across all three clinical trials. The trials concluded that potential future risk of a hernia accident should not contribute to an indication for surgical repair. Instead, relief of symptoms such as pain and other issues related to improvement of quality of life should be used as the metric to pursue surgical intervention. In the two studies with long-term results, the rate of crossover from WW to surgical repair was high (approximately 70%) due mostly to development of worsening pain.

Gong and colleagues recently performed a meta-analysis which included the short- and long-term follow-up data from the North American, UK, and Netherlands trials^[14]. Patients who underwent surgical repair reported significantly less pain with movement at a minimum of 12-month follow-up. However, there was no significant difference in the physical component score, mortality, surgical complications, or post-operative hernia recurrence between the WW and surgical repair groups. The meta-analysis confirmed that most patients will undergo an elective hernia repair operation within 10 years of presentation. Regardless, due to the low incidence of hernia accidents, the meta-analysis concluded that WW is a safe and acceptable option in short-term management of inguinal hernias in men. The authors also noted that WW provides a delay in surgery if desired but does not prevent relatively inevitable repair. Similar conclusions were reached by Reistrup^[15] and colleagues who recently published a systematic review of randomized and nonrandomized RCTs investigating watchful waiting.

TRIAL LIMITATIONS

Similar limitations were exhibited by all three clinical trials: generalizability, sample size, and length of follow-up. Most trial participants were white males, limiting extrapolation to patients of differing races and sexes. The authors of all trials reported that recruiting patients was difficult with only 45% and 69% of eligible patients agreeing to randomization in the North American and UK trials, respectively.

Additionally, it is important to note that clinical trials in low- and middle income countries are currently lacking. All trials completed to date are from high income countries, despite evidence that most hernias

Table 1. Comparison of Watchful Waiting Randomized Controlled Trials

Trial Location	Sample Size	Age	Short-Term			Long-Term		
			Follow-up	Crossover rate	Hernia Accidents	Follow-up	Crossover rate	Hernia Accidents
North American Trial	720	≥ 18 (mean 58)	3.2 years, mean	23% at 2 years	0.6% (<i>n</i> = 2)	11.5 years (max)	68% at 10 years	1.2% (<i>n</i> = 3)
United Kingdom Trial	160	> 55 (mean 70)	1.6 years, median	29%	1.3% (<i>n</i> = 1)	7.5 years (median)	72% at 7.5 years	2.5% (<i>n</i> = 2)
Netherlands Trial	496	> 50 (mean 65)	3 years	38%	2.3% (<i>n</i> = 6)	NA	NA	NA

worldwide occur in low-income countries and present at a later stage compared to those in developed countries. For example, in Guatemala one study suggested that as many as 25% of hernia cases may present at an emergent stage and that patient-related issues (i.e., lack of transport and follow-up) contribute greatly to significant delays in treatment^[16]. Thus, clinical trials completed in developed countries may fail to capture the total impact of hernia-related disease burden on patients in low-income countries.

CONCLUSION

Watchful waiting is a safe and appropriate early management strategy for male patients who present with asymptomatic or minimally symptomatic inguinal hernias. The risk of serious incarceration or strangulation is sufficiently low with an approach of watchful waiting. However, patients need to be informed that they will more likely elect to undergo surgical repair within a decade of diagnosis due to worsening pain. By delaying surgical intervention in patients with fewer or no complaints of pain, specific surgical complications such as post-herniorrhaphy inguinal groin pain that affect a minority of patients as well as the other common risks of surgery can be avoided, keeping in mind the overall incidences of pain in both the WW and surgical groups are the same. Our article has summarized the evidence obtained by three clinical trials in North America, the UK, and the Netherlands that support pursuing a watchful waiting strategy. We acknowledge that there is a concern on the part of some surgeons that patients will develop comorbidities with a WW approach, which may result in making these patients poor operative candidates. However, with the exception of a small number of patients from the UK trial who experienced cardiovascular symptoms, the majority of data from most trials do not support this notion. It is important to emphasize that these data apply only to males and that WW should not be extrapolated to females because the natural history of femoral hernias is different for males. Routine elective repair is still recommended in females.

DECLARATIONS

Authors' contributions

Made substantial contributions to overall concept and design of article: Fitzgibbons RJ, McBee PJ

Performed literature review: McBee PJ

Wrote text of manuscript: McBee PJ, Fitzgibbons RJ Jr

Edited manuscript: Fitzgibbons RJ Jr

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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

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Original Article

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Stapler vs. hand-sewn intrathoracic esophagogastric anastomosis: which anastomotic method renders better results?

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Abstract

Aim: We investigated the impact of the anastomotic method in the frame of open abdominothoracic esophageal resection (hand-sewn vs. stapler anastomosis) in patients with carcinoma submitted to surgery in the University Clinic of Saarland over a 14-year period.

Methods: In total, 176 patients underwent an abdominothoracic resection with intrathoracic anastomosis and conventional gastric conduit formation; two groups of patients were analyzed: end-to-end, hand-sewn anastomosis (Group 1) and end-to-side, circular stapler anastomosis (Group 2). Both groups were compared regarding anastomotic leaks and strictures, postoperative morbidity, 90-day mortality and survival.

Results: The rates of anastomotic leak and stricture in the stapler group were reduced in comparison to hand-sewn group, however without reaching statistical significance (8% vs. 13.5%, $P = 0.22$, and 6% vs. 13.5%, $P = 0.1$, respectively). In contrast, the rates of redo surgery (34.1% vs. 8%, $P = 0.001$) and 90-day mortality (11.9% vs. 2%, $P = 0.02$) were significantly higher in the hand-sewn anastomosis group.

Conclusion: The management of anastomotic leak (stent insertion vs. reoperation) combined with the use of stapler to perform intrathoracic esophagogastric anastomosis improved the postoperative outcome after abdominothoracic esophageal resection.



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Keywords: Esophagogastric anastomosis, circular stapler, Clavien-Dindo classification, anastomotic leak, gastric tube, esophagectomy, esophageal resection, Ivor-Lewis esophagectomy

INTRODUCTION

Esophageal cancer is a severe disease with poor prognosis. The reconstruction of alimentary tract after esophageal resection remains a challenge, with anastomotic leak being a main reason for major postoperative morbidity after abdominothoracic esophagectomy. The incidence of anastomotic leak varies from 0% to 24%^[1-4], leading to higher rates of postoperative morbidity and mortality^[5]. Various factors have been suggested to promote anastomotic leak, including patient-related characteristics^[6,7], perioperative factors^[8] and surgical technique (undo tension on the anastomosis, technical failures, adequacy of blood supply of both organs at the connection site^[9] and location of the esophagogastric anastomosis^[10]). Controversy remains about the optimal location of esophagogastric anastomosis (intrathoracic vs. cervical). Intrathoracic esophagogastric anastomosis has been associated with lower anastomotic leak rate, lower rate of recurrent nerve paresis and shorter hospital stay than a cervical anastomosis^[6,10,11]. However, three randomized controlled trials could not show statistical difference in anastomotic leak rate between intrathoracic and cervical location^[12-14]. Advantages of cervical anastomosis include wider oncologic resection margin and less devastating complications compared with intrathoracic anastomosis (risk of mediastinitis and esophagobronchial fistula). A potential solution to manage the challenge of intrathoracic esophagogastric anastomosis could be the use of a stapler device to perform the anastomosis; therefore, we focused on this topic of paramount importance in the present study. Since the first use of stapler anastomosis in 1979^[15], there have been several reports supporting its use in order to reduce the rate of anastomotic leak^[16,17]. Further technical variations, including the use of linear stapler to perform semi-mechanical intrathoracic anastomosis, have also been suggested to reduce postoperative anastomotic leak rate^[18]. We investigated the impact of anastomotic method (hand-sewn vs. circular stapler) on anastomotic leak rate in patients with esophageal carcinoma submitted to intrathoracic esophagogastric anastomosis in the University Clinic of Saarland during a 14-year period.

METHODS

We performed a retrospective, non-randomized study to investigate which anastomotic method rendered better results. Our study population consisted of 176 patients with esophageal carcinoma, with intrathoracic anastomosis after abdominothoracic resection. We performed an Ivor-Lewis abdominothoracic esophageal resection, consisting of a median laparotomy, mobilization of the stomach and preparation of a conventional gastric tube. Simultaneous cholecystectomy was routinely performed^[19]. The gastric conduits were performed conventionally^[20] (three patients submitted to fundus rotation gastropasty to achieve longer gastric conduit and better blood supply^[9] were excluded). For conventional tube formation, the lesser curvature with the vessel arcade was resected with linear stapler^[21]. The right gastric and gastroepiploic vessels provide the blood supply of the gastric conduit. A right anterolateral thoracotomy was performed, and the esophageal resection was performed in the level of azygos vein. D2 lymphadenectomy was routinely performed. Patients were divided into two groups: Group 1 received hand-sewn, double row, end-to-end anastomosis using 4-0 PDS and 5-0 PDS stitches and Group 2 received single row end-to-side, stapler anastomosis using a 25-mm circular stapler. The type of anastomosis was selected upon surgeon's preference. Anastomosis was mainly performed as hand-sewn from 2001 to 2012 and changed to a stapler anastomosis routinely using the 25-mm circular intraluminal stapler (Covidien, EEA, DST Series). Operations were only performed by chief or experienced senior surgeons.

Both groups were compared regarding anastomotic leaks and strictures, postoperative morbidity, 90-day mortality and survival.

To assess the severity of perioperative morbidity, the Clavien-Dindo classification was used^[22]; the overall postoperative morbidity during first hospital stay (surgical and respiratory complications included) was divided into minor morbidity, corresponding to Clavien-Dindo Grades I-II, and major/lethal postoperative morbidity corresponding to Clavien-Dindo Grades III-V. The group of minor postoperative morbidity consisted of complications treated conservatively. The group of major postoperative morbidity consisted of complications requiring surgical, endoscopic or radiological intervention (Clavien-Dindo Grade III); life-threatening complications requiring ICU management (Grade IV); and lethal complications (Grade V). The mortality during the first hospital stay was divided into 30-, 60- and 90-day mortality.

The disruption of the anastomosis leading to extravasation of intraluminal content was defined as anastomotic leak. The definite diagnosis of anastomotic leak was confirmed endoscopically. Data collection and analysis were performed only on patients who underwent an intrathoracic anastomosis.

Anastomotic stricture was defined as dysphagia in the 6-month endoscopic control requiring intervention (endoscopic dilatation). Patients with anastomotic stricture suffered from Clavien-Dindo Grade III complication.

Tumor management

Endoscopy was performed preoperatively as well as 6 months postoperatively to exclude tumor recurrence. In the preoperative work-up, a computed tomography was performed to detect further organ metastases. Neoadjuvant therapy was carried out preoperatively according to the international guidelines^[23]. Surgical resection followed 4-6 weeks after the end of the neoadjuvant therapy. Until 2012, we used the PLF scheme, based on cisplatin, folic acid, 5-fluoruracil and simultaneous irradiation [45 Gy (1.5 Gy per day)] in cases of squamous-cell esophageal carcinoma. Since 2012, we have performed neoadjuvant chemoradiation, as proposed by the Dutch CROSS trial, consisting of weekly administration of carboplatin und paclitaxel for 5 weeks and concurrent radiotherapy (41.4 Gy in 23 fractions) followed by surgery 4-6 weeks later. Cardiopulmonary examinations (electrocardiogram, echocardiogram and lung function test) were performed preoperatively.

Perioperative treatment

Patients received single-shot antibiotics intraoperatively. This included metronidazole 500 mg i.v. and ceftriaxone 2 g i.v. In the case of penicillin allergy, clindamycin 600 mg i.v. was injected. After confirmation of a patent anastomosis-using radiographic control-on Postoperative Day 5, the nasogastric tube was routinely removed. Then, enteral feeding including liquids was started.

Statistical analysis

Statistical analysis was performed using χ^2 test (chi square test), binary logistic regression and Mann-Whitney *U* test. Survival data were recorded contacting either the Cancer Registry of Saarland or the house physicians. A 6-month follow-up was routinely performed including endoscopy. Log rank test and Cox regression were performed for survival analysis. Statistical analysis was conducted using IBM SPSS Statistics V22.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics, operative data and postoperative outcome

Overall, 126 (71.6%) patients (Group 1) received a hand-sewn anastomosis, while 50 (28.4%) patients (Group 2) received a stapler anastomosis. Patient characteristics were similar in both groups [Table 1]. Median age of patients at the time of surgery was 61 years (34–88 years), with a male-to-female ratio of 153:23. Fifty-two (29.5%) patients were diagnosed with squamous-cell esophageal cancer, and 124 (70.5%) patients with esophageal adenocarcinoma. Forty-five (25.6%) patients had chronic obstructive pulmonary disease (COPD) at the time of surgery, 33 (18.9%) patients coronary heart disease (CHD) and 34 (19.3%) patients were obese. The preoperative rates of COPD ($P = 0.13$), CHD ($P = 0.20$) and obesity ($P = 0.42$) were not significantly different between the groups. In total, 93 (52.8%) patients were admitted to neoadjuvant therapy due to preoperative staging (Group 1: 47.6% vs. Group 2: 66%, $P = 0.11$).

Median duration of surgery was 269 min (128–532 min), whereas the median intraoperative blood loss was 300 mL (5–4000 mL), as shown in Table 2. The median harvest of dissected lymph nodes was 17 (3–62).

Minor postoperative complications (Clavien-Dindo Grades I–II) were presented in 23 (13%) patients. Major postoperative complications (Clavien-Dindo Grades III–IV) appeared in 29 (16.5%) patients. Thirteen (10.3%) patients in Group 1 and 10 (20%) patients in Group 2 suffered from minor complications, whereas 25 (19.8%) patients in Group 1 and 4 (8%) patients in Group 2 suffered from major complications [Table 2]. More specifically, in Group 1, the distribution of minor complications was as follows: 2 (0.015%) patients with wound infection, 3 (0.02%) with chyle leak, 3 (0.02%) with pneumonia and 5 (0.04%) with pleural effusion. In Group 2, the distribution of minor complications was as follows: 1 (0.02%) patient with wound infection, 1 (0.02%) with chyle leak, 4 (8%) with pneumonia, 6 (0.06%) with pleural effusion and 1 (0.02%) with pneumothorax. The distribution of major complications in Group 1 was as follows: 4 (0.03%) patients with anastomotic leak, 4 (0.03%) with anastomotic leak and simultaneous gastric conduit necrosis, 5 (0.04%) with anastomotic leak and concomitant mediastinitis, 5 (0.04%) with anastomotic leak and respiratory insufficiency, 1 (0.008%) patient with bile leak, 1 (0.008%) with early hiatal hernia, 3 (0.02%) with wound dehiscence and 2 (0.015%) with chyle leak needing reoperation. There were 4 (8%) patients with anastomotic leak in the stapler anastomosis group. Eighteen (10.2%) patients suffered from lethal postoperative complication (Clavien-Dindo Grade V) within 90 days after surgery. There were no significant differences between both groups concerning the incidence of minor and major morbidity, however the 90-day mortality was higher in the hand-sewn anastomosis group ($P = 0.02$, Table 2).

Minor surgical complications included wound infection and chyle leak treated conservatively, while minor cardiopulmonary complications included pleura effusion treated with diuretics, pneumothorax with no need for draining tube, pneumonia and atrial fibrillation. The minor postoperative morbidity did not differ significantly between the groups ($P = 0.2$). Major surgical complications included necrosis of gastric conduit enterothorax, hiatal hernia, anastomotic leak, wound dehiscence, bile leak (occurring in one patient in the frame of prophylactic cholecystectomy) and chyle leak with need for reoperation. Surgical complications (anastomotic leak and necrosis of the gastric conduit) led predominantly to major and lethal postoperative morbidity (Clavien-Dindo Grades III–V).

Forty-seven (26.7%) patients were subjected to redo surgery during the first hospital stay. The rate of reoperations differed substantially between both groups (Group 1: 34.1% vs. Group 2: 8%, $P = 0.001$). The incidence of anastomotic leak was 12.5% (22/176) and did not differ significantly between the groups (Group 1: 14.3% vs. Group 2: 8%, $P = 0.22$), although it was almost 50% reduced in the stapler anastomosis group. The median hospital stay was 20 days (9–198 days) and did not significantly differ between the

Table 1. Esophagectomies with intrathoracic anastomosis for esophageal cancer (n = 176): patient characteristics

Characteristic	Hand-sewn 126	Stapler 50	Total 176	P value
Age in years, median [min, max]	62 [42, 88]	61 [34, 84]	61 [34, 84]	0.34
Men/women ratio n (%)	111/15 (88%/12%)	42/8 (84%/16%)	153/23 (86.9%/13.1%)	0.23
Adenocarcinoma of esophagus n (%)	86 (68.3%)	38 (76%)	124 (70.5%)	0.21
Squamous-cell carcinoma of esophagus n (%)	40 (31.7%)	12 (24%)	52 (29.5%)	0.21
COPD n (%)	35 (27.8%)	10 (20%)	45 (25.6%)	0.13
Coronary heart disease n (%)	26 (20.6%)	7 (14%)	33 (18.9%)	0.20
Obesity n (%)	24 (19%)	10 (20%)	34 (19.3%)	0.42
Neoadjuvant therapy n (%)	60 (47.6%)	33 (66%)	93 (52.8%)	0.11

Chi-square and Mann-Whitney *U* tests were respectively used.

Table 2. Esophagectomies with intrathoracic anastomosis for esophageal cancer (n = 176): operative data and postoperative outcome

Parameters	Hand-sewn 126	Stapler 50	Total 176	P value
Duration of surgical procedure median [min, max]	280 [128, 532]	261 [160, 376]	269 [128, 532]	0.49
Blood loss in mL median [min, max]	300 [50, 4000]	200 [5, 1500]	300 [5, 4000]	0.12
Number of dissected lymph nodes, median [min, max]	17 [3, 62]	17 [6, 34]	17 [3, 62]	0.59
Minor postoperative complications Clavien-Dindo Grade I-II, n (%)	13 (10.3%)	10 (20%)	23 (13%)	0.2
Major postoperative complications Clavien-Dindo Grade III-IV, n (%)	25 (19.8%)	4 (8%)	29 (16.5%)	0.12
Reoperation, n (%)	43 (34.1%)	4 (8%)	47 (26.7%)	0.001***
Respiratory complications, n (%)	35 (27.8%)	12 (24%)	47 (26.3%)	0.36
Anastomotic leak, n (%)	18 (14.3%)	4 (8%)	22 (12.5%)	0.22
Anastomotic stricture, n (%)	17 (13.5%)	3 (6%)	20 (11.4%)	0.1
30-day mortality, n (%)	6 (4.8%)	0 (0%)	6 (4.8%)	0.13
60-day mortality, n (%)	12 (9.6%)	1 (2%)	13 (7.4%)	0.08
90-day mortality, n (%)	17 (13.5%)	1 (2%)	18 (10.2%)	0.02*
Hospital stay in days, median [min, max]	21 [9, 198]	18 [12, 114]	20 [9, 198]	0.26

* $P < 0.05$, *** $P < 0.001$; Chi-square and Mann-Whitney *U* tests were respectively used.

groups ($P = 0.26$). The rate of anastomotic stricture in the 6-month follow-up did not significantly differ between the groups (Group 1: 13.5% vs. Group 2: 6%, $P = 0.1$), although it was more than 50% reduced in the stapler group. The 30-, 60- and 90-day mortality was 4.8% ($n = 6$), 7.4% ($n = 13$) and 10.2% ($n = 18$), respectively. The 90-day mortality was significantly lower in Group 2 (Group 1: 13.5% vs. Group 2: 2%, $P = 0.02$). The most apparent differences of surgical outcome when comparing the anastomotic methods were the rate of reoperation and consequently the 90-day mortality [Table 2].

Management of anastomotic leak

In the stapler anastomosis group, anastomotic leaks were treated with endoscopic stent insertion: 4 out of 50 (8%) patients after stapler anastomosis suffered from anastomotic leak, of whom only one was subjected to new surgical procedure and 3 were successfully treated with endoscopic stent insertion. In contrast, in the hand-sewn anastomosis group, anastomotic leaks were predominantly treated with reoperation: 18 patients after hand-sewn anastomosis suffered from anastomotic leak, of whom 14 underwent new surgical procedure and 4 were treated with endoscopic stent insertion. Consequently, 90-day mortality (Clavien-

Dindo Grade V complications) and overall survival were statistically significantly different between the groups of patients.

Risk factors for major and lethal postoperative complications (Clavien-Dindo Grades III-V) after abdominothoracic esophageal resection

The type of anastomosis ($P = 0.004$) and duration of surgery ($P = 0.002$) significantly influenced the incidence of major and lethal postoperative complications (Clavien-Dindo Grades III-V) in the multivariate analysis (binary logistic regression, [Table 3](#)).

Survival

Overall median patient survival was 18 months (0-121 months). In Group 1, the median survival was 16 months [minimum: 0; maximum: 119; mean: 31; Standard Deviation (SD): 32], whereas, in Group 2, the median survival was 22 months (minimum: 1; maximum: 121; mean: 20; SD: 18). Patients subjected to hand-sewn anastomosis experienced worse overall survival, as did patients with advanced UICC tumor stage ($P = 0.001$ and $P = 0.002$, respectively, log rank test), as shown in [Table 4](#) and [Figure 1](#). No significant differences were observed between UICC tumor staging and anastomotic technique ($P = 0.355$) or between histological type and anastomotic technique ($P = 0.175$).

In the multivariate analysis, the type of anastomosis and advanced UICC tumor stage were independent factors that significantly influenced overall survival [[Table 5](#) and [Figure 2](#)].

DISCUSSION

In the present study, we focused on the impact of anastomotic method (intrathoracic stapler *vs.* hand-sewn esophagogastric anastomosis) on surgical outcome after abdominothoracic esophagectomy for cancer. Our data suggest that the management of anastomotic leak (endoscopic stent insertion *vs.* reoperation), combined with the use of stapler to perform intrathoracic esophagogastric anastomosis, positively influences postoperative morbidity, mortality and overall survival.

Regarding anastomotic leak rates after abdominothoracic esophageal resection, our incidence of 12.5% is similar to other reported rates. Major/lethal postoperative complications (Clavien-Dindo Grades III-V) were significantly lower in the stapler anastomosis group, obviously due to the lower reoperation rate. It is important to note that, in the hand-sewn anastomosis group, anastomotic leaks were treated with new surgical procedure (14 out of 18 patients with anastomotic leak), contrary to the stapler anastomosis group, thus leading to higher mortality (34.1% reoperation and 13.5% Clavien-Dindo Grade V complications in the hand-sewn anastomosis group, compared to 8% and 2% in the stapler group, respectively). In the same line of evidence, no patient died from anastomotic leak in the stapler anastomosis group due to successful treatment with endoscopic stent insertion. This fact implies that the aggressive management of anastomotic leaks with redo surgery in the hand-sewn anastomosis group significantly worsened the postoperative outcome. In addition, we cannot exclude that the change of the intrathoracic anastomosis method (end-to-end *vs.* end-to-side) may have influenced the postoperative outcome, as the end of the gastric conduit is the most ischemic part. However, the intrathoracic esophagogastric anastomosis was performed in the height of azygos vein; the tension of the anastomosis is not so high; and the risk of gastric conduit ischemia is lower compared to, for example, in a cervical esophagogastric anastomosis. Therefore, it remains unclear whether the manner of anastomosis substantially influenced the incidence of anastomotic leaks. Moreover, the esophagogastric anastomosis was sewn from 2001 to 2012, and stapled anastomosis predominated thereafter; the era effect cannot be estimated in the significant improvement in outcomes. Both intraoperative blood loss and duration of surgery were comparable between the groups, but lower in the stapler group, in accordance with the results of other observational studies claiming that stapler anastomosis

Table 3. Univariate and multivariate analysis of predictors of major postoperative complications (Clavien-Dindo III-IV) after resection for esophageal cancer

Parameter	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.022 (0.998-1.057)	0.200		
Sex	1.745 (0.703-4.331)	0.230		
CHD	1.847 (0.838-4.071)	0.130		
COPD	1.633 (0.802-3.327)	0.180		
Obesity	1.057 (0.465-2.403)	0.900		
Neoadjuvant therapy	0.984 (0.486-1.993)	0.964		
Duration of surgery	0.992 (0.987-0.997)	0.003**	0.991 (0.986-0.997)	0.002**
Type of anastomosis (hand-sewn vs. stapler)	3.296 (1.369-7.937)	0.008**	3.666 (1.499-8.963)	0.004**
Intraoperative blood loss	1.000 (0.999-1.001)	0.68		

**P < 0.01. OR: Odds ratio; CI: confidence interval; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease.

Table 4. Risk factors for worse overall survival after abdomino-thoracic resection with intrathoracic anastomosis for esophageal cancer-univariate analysis

Parameter	Log rank for categorical parameters		Cox regression for continuous parameters	
	P value	χ^2	OR (95%CI)	P value
Age			1.07 (0.997-1.036)	0.098
Sex	0.528	0.398		
CHD	0.950	0.004		
COPD	0.153	2.039		
Obesity	0.118	2.446		
Neoadjuvant therapy	0.060	3.595		
Duration of surgery			1.002 (0.999-1.004)	0.197
Type of anastomosis (hand-sewn vs. stapler)	0.001***	22.866		
Anastomotic leak	0.790	0.070		
Reoperation	0.150	2.108		
Intraoperative blood loss			1.000 (0.999-1.000)	0.658
Minor postoperative complication (Clavien-Dindo I-II)	0.810	1.060		
Major postoperative complication (Clavien-Dindo III-V)	0.100	0.001		
Histology (SCC vs. adenocarcinoma)	0.310	1.034		
UICC tumor stage	0.002**	16.971		

P < 0.01, *P < 0.001. OR: Odds ratio; CI: confidence interval; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; SCC: squamous cell carcinoma; UICC: Union international contre le cancer.

is faster than hand-sewn anastomosis^[24].

There are numerous other studies comparing hand-sewn with stapled esophagogastric anastomosis. The majority consist in retrospective, non-randomized studies. Primary end points in these studies were anastomotic leak and stricture rate. The reported results are not unanimous. Several reports showed no difference in anastomotic leak comparing both anastomotic methods, while other reports demonstrated decreased anastomotic leaks with stapler anastomosis. Kim *et al.*^[24] concluded in their systematic review of eight randomized, controlled trials that there was no significant difference in the anastomotic leak or early

Table 5. Risk factors for survival after abdomino-thoracic resection for esophageal cancer-multivariate analysis

Parameter	Cox regression	
	OR (95%CI)	P value
Type of anastomosis	0.165 (0.067-0.409)	< 0.001***
UICC tumor stage	1.371 (1.130-1.663)	0.001***

*** $P < 0.001$. OR: Odds ratio; CI: confidence interval; UICC: Union international contre le cancer.

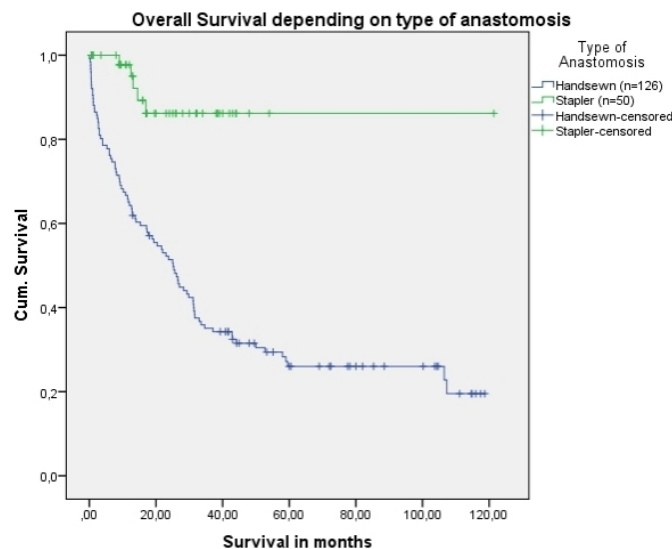


Figure 1. Cumulative survival after abdomino-thoracic resection with intrathoracic anastomosis for esophageal cancer depending upon the type of anastomosis ($P < 0.001$, log rank test).

mortality between the anastomotic methods. One study demonstrated a difference in stricture rates, with fewer after hand-sewn anastomosis (9% vs. 40%, $P = 0.003$)^[25]. Two meta-analyses found no significant difference in the rate of anastomotic leak comparing both anastomotic techniques. However, there are strong limitations to mention: variability of performed surgical procedures, stapler size, end-to-end vs. end-to-side esophagogastric anastomosis, cervical vs. intrathoracic anastomosis, one-row vs. double-row anastomosis and application of neoadjuvant therapy prior to surgery. Our results show no significant differences concerning anastomotic leaks and strictures between both types of anastomosis, however both occurred less frequently (with a 50% reduction) after stapler anastomosis. Moreover, we should also note that the 30-day mortality (often used in previous studies) underestimates in-hospital mortality. Our data also indicate that 90-day mortality more accurately represents the in-hospital mortality. The 90-day mortality was significantly reduced after stapler anastomosis (2% vs. 13.5%).

Simultaneous cholecystectomies were performed in the study period routinely, in order to avoid symptomatic gallstone formation later. Since 1947, it has been hypothesized that there is an increased rate for gallstone formation after gastric surgery^[26], as a result of resection of the anterior branch of the vagal nerve interrupting gallbladder innervation, thus disturbing gallbladder emptying and increasing cholecystokinin release^[27-29]. Gillen *et al.*^[30] showed that the benefit of simultaneous cholecystectomy in the frame of gastric/esophageal resection does not outweigh the risks, thus not supporting the hypothesis of prophylactic cholecystectomy. This suggestion was based on the 6% incidence of acute/late cholecystectomy and the higher calculated additional morbidity of 0.95% compared with 0.45%^[30]. One out of the 176 (0.005%) patients of our study group was submitted to redo surgery because of biliary leak after

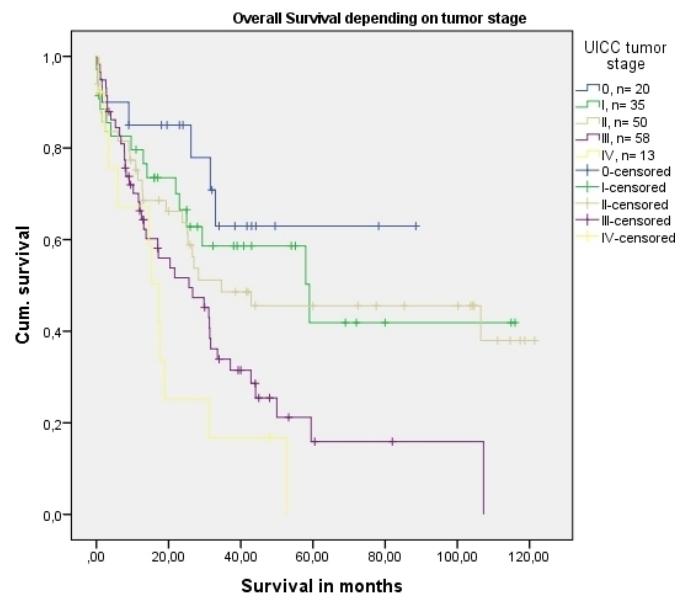


Figure 2. Cumulative survival after abdomino-thoracic esophageal resection with intrathoracic anastomosis for cancer depending upon UICC tumor stage ($P = 0.001$, log rank test).

prophylactic cholecystectomy in the frame of esophageal resection, thus not adding substantial morbidity.

The advantages of the present study are the qualitative homogeneity of the included patients and the thorough analysis of numerous parameters. We chose to include in the analysis only patients subjected to open Ivor-Lewis abdominothoracic esophageal resection with intrathoracic anastomosis. The therapeutic protocol used in our department is also standardized and given in detail. A thorough comparison of various parameters including intraoperative blood loss, duration of surgical procedure, number of reoperations, 30-, 60- and 90-day mortality and overall survival was performed.

The limitations of the present study are its retrospective, non-randomized character and the fact that the numbers of hand-sewn and stapler esophagogastric anastomoses are not equal (126 vs. 50). The management of anastomotic leaks changed during the different time periods, from being more aggressive (redo surgery) in the past to more conservative now (stent insertion), partially explaining the better postoperative outcome in the stapler anastomosis group.

In summary, the use of stapler to perform esophagogastric anastomosis and endoscopic stent insertion to manage anastomotic leak improved the postoperative outcome after abdominothoracic esophageal resection with intrathoracic anastomosis. In the current study, we experienced a lower anastomotic leaking rate and a better overall survival in favor of the group of patients who underwent a circular stapler anastomosis. Further improvement of surgical technique (minimally invasive surgical procedures) and better perioperative care protocols should further minimize anastomotic leaks after esophageal resections for cancer.

DECLARATIONS

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Authors' contributions

The first author: Kolokotronis T

The last author: Galanis 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

Not applicable.

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Review

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Therapeutic EUS

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Abstract

Currently, the standard treatment for pancreatic neoplasms is surgical resection. However, pancreatic surgical resection is associated with high morbidity and mortality. Patients unfit for surgery are undergoing regular cross-sectional imaging surveillance. Controversy surrounds the optimal surveillance of patients with pancreatic neoplasms, underlying the need for minimally invasive treatment modalities as an alternative to surgical treatment. To date, endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is an emerging minimally invasive therapeutic alternative to surgical resection for various pancreatic neoplasms. We review evaluations of EUS-RFA for various pancreatic neoplasms to better understand its effectiveness and safety.

Keywords: Pancreatic neoplasm, endoscopic ultrasound, radiofrequency ablation

INTRODUCTION

Endoscopic ultrasound (EUS) is widely used to diagnose biliopancreatic diseases. The development of EUS-guided fine needle aspiration (EUS-FNA) in the early 1990s has expanded EUS-guided interventions. After the development of the linear echoendoscope and the increasing sizes of the EUS devices' working channels, EUS has recently evolved to become a therapeutic method for patients with biliopancreatic disease^[1].

Although surgical resection has been the only curative treatment for various pancreatic tumors, pancreatic surgery is related with high morbidity and mortality^[2,3]. The recent advance of the EUS device has led to an increase in EUS-guided local treatment for pancreatic tumors. Radiofrequency ablation (RFA) is a local



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treatment that uses heat energy generated by the agitation of ions in cells to induce cell death and coagulation necrosis^[4]. RFA has been widely used to treat solid tumors in organs such as the liver, lungs, and kidneys. Recently, EUS-RFA has been described as an effective and safe new therapeutic modality for treating pancreatic neoplasms. We review EUS-RFA for pancreatic neoplasms and its outcomes.

POTENTIAL INDICATIONS

Currently, there are no established indications of EUS-RFA. However, EUS-RFA can be used for various tumors, including benign solid pancreatic tumors, such as neuroendocrine tumors and insulinomas^[5-7], pancreatic cystic tumors^[6], and pancreatic cancers^[8,9]. There is no absolute contraindications of EUS-RFA. However, as previously reported, there is the possibility that severe adverse events may develop when EUS-RFA is applied to pancreatic lesions close to the main pancreatic duct^[5,10]. Therefore, it may be considered as a relative contraindication of EUS-RFA.

MATERIALS AND INSTRUMENTS

1. An oblique-viewing therapeutic curvilinear array echoendoscope.
2. Radiofrequency (RF) generator [Figure 1].
3. Radiofrequency ablation (RFA) probes: The currently available RFA probes are EUSRA RF electrodes (STARmed, Koyang, Korea), Habib™ EUS-RFA catheters (EMcision Ltd., London, UK), 19-gauge EUS-FNA needle electrodes (Radionics, Inc., Burlington, MA, USA), and hybrid cryotherm probes (Hybrid-Therm®; ERBE, Tübingen, Germany). EUS-RFA probes are classified as “through the needle” type and “EUS-RFA needle” type. Habib EUS-RFA catheter is a “through the needle” type and the remaining three probes are “EUS-RFA needle” types. Among these probes, the Hybrid cryothermal probe is bipolar and the rest are monopolar probes. All probes are connected to the RF generator to deliver heat energy to the target lesions.
4. Ultrasound contrast agents (UCAs): UCAs are useful for identifying remnant tumors, evaluation of early treatment responses, and an accurate guidance for additional ablation^[11].

TECHNIQUE

Prophylactic antibiotics are administered intravenously before EUS-RFA. An RFA probe is inserted into the target lesion under EUS-guidance to avoid major vessels or the pancreatic or bile ducts [Figure 2A]. Ablation is usually started at the far end inside the lesion [Figure 2B]. After the needle tip is identified within the margin of the tumor on EUS, the RF generator is activated to deliver energy [Figure 2C]. After a lag period, echogenic bubbles gradually start appearing around the needle, indicating effective ablation at the site [Figure 2D]. The size of the ablation zone depends on the wattage, RFA needle tip length, and time duration. For the ablation of large lesions, the electrode may be repositioned under EUS visualization to ablate another zone along the same trajectory closer to the echoendoscope while staying away from the gut wall. A fanning technique allows additional needle passes to further ablate different areas within the same lesion.

RFA-related adverse events are closely related with thermal injury to the pancreatic parenchyma and surrounding structures, including blood vessels, bile ducts, the stomach, and the duodenum. Technical precautions are required for preventing thermal injury to adjacent organs, including maintenance of a 5-mm minimum safety margin from the surrounding vessels and a step-up approach for ablation of larger

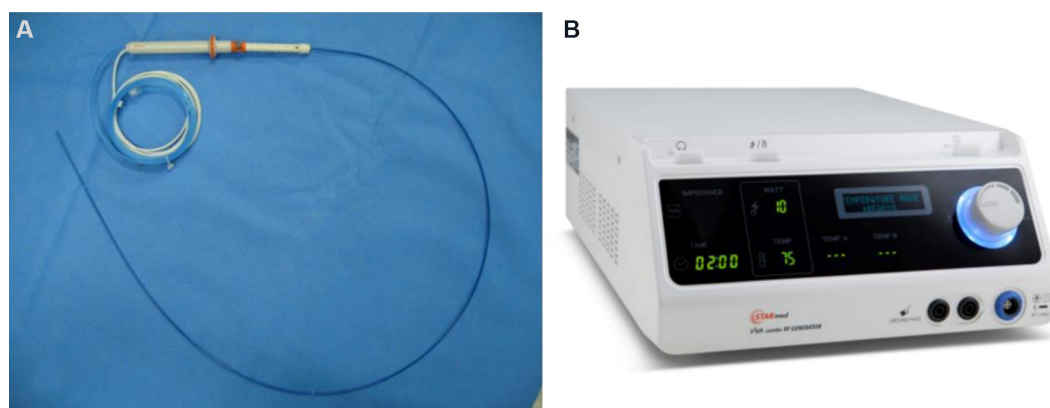


Figure 1. Endoscopic radiofrequency electrode and power generator (STARmed, Koyang, Korea): 19-gauge endoscopic radiofrequency ablation electrode (A); and a VIVA radiofrequency power generator (B).

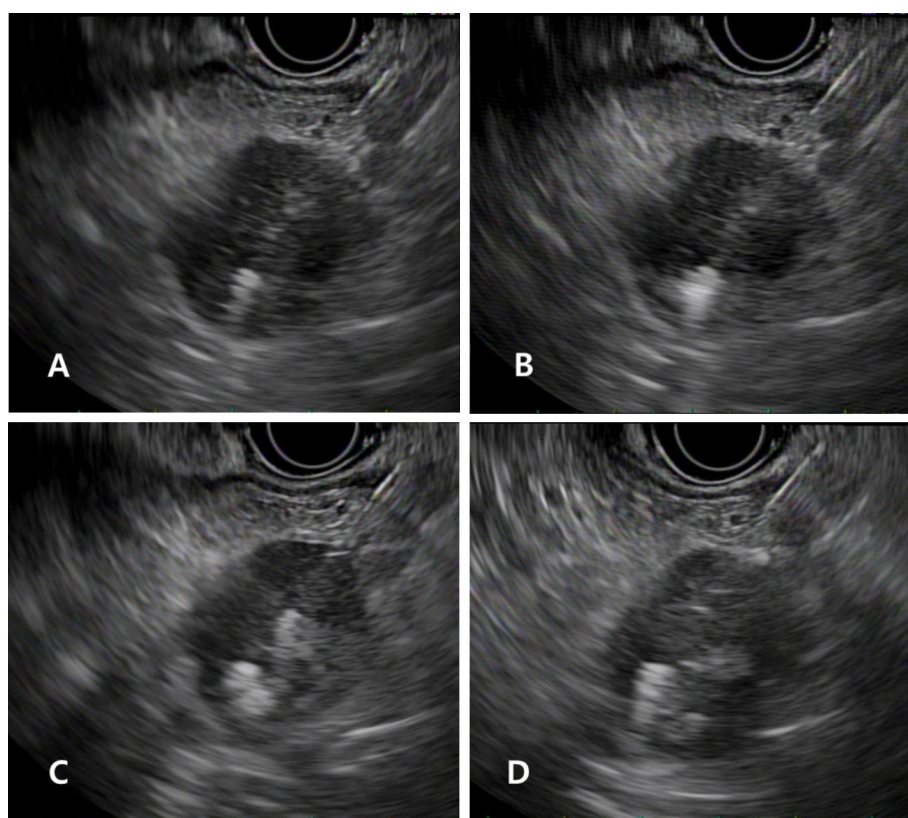


Figure 2. Image of EUS-RFA: a 19-gauge needle probe is inserted into the pancreatic tumor under EUS-guidance (A); ablation is usually started in the right distal part of the tumor on the EUS image at the far end inside the lesion (B); echogenic bubbles are identified around the needle after ablation (C); and after needle withdrawal and reinsertion into the mass, RFA is repeated on the left side of the previous ablation site (D). EUS-RFA: Endoscopic ultrasound-guided radiofrequency ablation.

tumors (> 2 cm in diameter)^[5].

After the initial session of EUS-RFA, early treatment response can be evaluated by contrast-enhanced-EUS (CE-EUS)^[11]. CE-EUS is helpful for differentiating viable tumors after ablation and targeting remnant viable tumors. When a viable tumor is identified on the CE-EUS, a second RFA session can ablate remnant tumors

[Figure 3].

DISCUSSION

Outcomes of EUS-RFA in benign solid pancreatic tumor

Since Goldberg *et al.*^[12] first reported EUS-RFA for the pancreas in a porcine model in 1999, several studies have demonstrated its effectiveness for various pancreatic tumors. Table 1 summarizes the clinical outcomes of previous research.

In a study by Lakhtakia *et al.*^[7], EUS-RFA was performed in three patients with symptomatic pancreatic insulinoma using an internally cooled prototype needle electrode (EUSRA, STARmed). After ablation of pancreatic insulinoma, symptomatic relief with biochemical improvement was achieved in all patients, and patients were followed-up without symptoms for 12 months. In a prospective study by Choi *et al.*^[5], 10 patients with benign solid pancreatic tumors [nonfunctional neuroendocrine tumor (NET), $n = 7$; solid pseudopapillary neoplasm, $n = 2$; and insulinoma, $n = 1$] underwent EUS-RFA. After 16 EUS-RFA sessions, a radiologic complete response was identified in seven patients during a median follow-up of 13 months [Figure 4].

In a study by Barthet *et al.*^[13], 12 patients with 14 NET underwent EUS-RFA. At the 1-year follow-up, 12 NETs showed complete response or lesion necrosis (86%). Oleinikov *et al.*^[14] performed ablation on 18 patients (NET, $n = 11$; and insulinoma, $n = 7$) with 27 lesions. All patients with insulinoma demonstrated complete relief of hypoglycemia-associated symptoms and normalization of glucose levels was observed 1 h after RFA. Radiologic complete response was achieved in 96.3% of patients (17 of 18) during a median of 8.7 months without clinically significant recurrence. In 2020, de Nucci *et al.*^[15] reported a prospective study on EUS-RFA in 10 patients with 11 NETs. At the 12-month follow-up, all lesions demonstrated complete disappearance with radiological normalization. A systemic review of published research on EUS-RFA for NETs, including 12 studies and 61 patients with 73 tumors, showed an overall effectiveness rate of 96% (75%-100%) in a mean follow-up period of 11 months (1-34 months) and an adverse event rate of 13.7%, with no serious adverse events^[16]. In this review, a larger tumor was related with treatment failure (mean size in the non-response group was 21.8 ± 4.71 mm vs. a mean size of 15.07 ± 7.34 mm in the response group, $P = 0.048$). According to the ROC curve, a NET of size ≤ 18 mm at EUS was associated with a positive response to EUS-RFA, with a sensitivity of 80% (95%CI: 28.4%-99.5%), a specificity of 78.6% (95%CI: 63.2%-89.7%), and an AUC of 0.81 (95%CI: 0.67-0.95). EUS-RFA is an effective and safe treatment for benign pancreatic tumors. However, the long-term outcomes are not well described. As solid pancreatic tumors are slow to grow and have the potential of malignant transformation, long-term follow-up data are mandatory to evaluate the outcomes of EUS-RFA.

Currently, EUS-guided ethanol ablation is most commonly used for treating pancreas cystic lesions. Although the application of EUS-guided ethanol ablation for solid pancreatic tumors is limited, few reports have demonstrated that EUS-guided ethanol ablation is effective and safe for treating benign solid pancreatic tumors. In a study by Paik *et al.*^[17], 8 patients with borderline malignant pancreatic tumors underwent EUS-guided ethanol ablation (insulinoma, $n = 3$; nonfunctioning NET, $n = 2$; solid pseudopapillary neoplasm, $n = 2$; and insulinoma, $n = 1$). After ethanol ablation, 6 patients (75%) achieved treatment success. However, 2 patients still had persistent tumors. One patient experienced severe pancreatitis after ablation. Among 6 patients who achieved initial treatment success, 1 patient experienced tumor recurrence within 15 months. In a recent prospective study by Choi *et al.*^[18], 33 patients who had 40 pathologically confirmed pancreatic NET (< 2 cm in diameter) underwent 63 sessions of EUS-guided ethanol-lipiodol ablation. Complete ablation was achieved in 24 of 40 tumors (60%), with 1 (18 tumors,

Table 1. Summary of published data on EUS-RFA

Ref. (year)	Indications and number of patients	RF devices	Mean tumor size (range)	Application power and time	Mean RF sessions	Technical success	Treatment response	Follow-up periods	Adverse events
Pai <i>et al.</i> ^[19] (2015)	Mucinous cyst (4), IPMN (1), microcystic adenoma (1), NET (2)	Habib EUS-RFA catheter	Pancreas cyst: 36.5 (24-70), NET: 27.5 (15-40)	5-25W, 90-120s	1.3 (1-2)	100%	Pancreas cyst: complete resolution (2, 33%), size reduction (4, 67%), NET: 50% reduction with vascular changes (2, 100%)	3-6 months	Mild abdominal pain (2, 25%)
Lakhtakia <i>et al.</i> ^[7] (2016)	Insulinoma (3)	EUSLA	19 (14-22)	50W, 10-15s	1	100%	Complete resolution of hypoglycemia (3, 100%)	11-12 months	None
Song <i>et al.</i> ^[8] (2016)	Locally advanced pancreatic cancer (4), metastatic pancreatic cancer (2)	EUSLA	38 (30-90)	20-50W, 10s	1.3 (1-2)	100%	Necrosis at the ablation site (6, 100%)	2-6 months	Mild abdominal pain (2, 33%)
Scopelliti <i>et al.</i> ^[9] (2018)	Locally advanced pancreatic cancer (10)	EUSLA	49.2 (35-75)	20-30W, 100-560s	1.4 (1-2)	100%	Necrosis at the ablation site (10, 100%)	30 days	Mild abdominal pain (2, 20%), ascites (2, 20%), peripancreatic effusion (2, 20%)
Choi <i>et al.</i> ^[5] (2018)	NET (7), solid pseudopapillary neoplasm (2), insulinoma (1)	EUSLA	20 (8-28)	50W	1.6 (1-3)	100%	Radiologic complete response (7, 70%)	Median 13 months	Mild abdominal pain (1, 10%), acute pancreatitis (1, 10%)
Barthet <i>et al.</i> ^[13] (2019)	IPMN (16), MCN (1), NET (14 lesions in 12)	EUSLA	PCL: 28 (9-60), NET: 13.1 (10-20)	50W	NA	100%	NET: radiologic complete response (12, 86%) Pancreas cyst: complete response (11, 65%), more than 50% reduction (1, 6%)	12 months	Acute pancreatitis (1, 3%), jejunal perforation (1, 3%), main pancreatic duct obstruction (1, 3%)
Oleinikov <i>et al.</i> ^[14] (2019)	NET (18 lesions in 11 patients), insulinoma (9 lesions in 7 patients)	EUSLA	14.3 (4.5-30)	10-50W, 5-12s			NET: radiologic complete response (17 lesions, 94%) Insulinoma: complete resolution of hypoglycemia with normalization of glucose levels (7 patients, 100%)	Mean 8.7 ± 4.6 months (range 2-21 months)	Acute pancreatitis (2, 11%)
Oh <i>et al.</i> ^[20] (2020)	Microcystic SCN (13)	EUSLA	50 (34-52.5)	50W	1.46 (1-2)	100%	Partial response (8, 61.5%)	Median 9.21 months (IQR 4.79-32.39)	Abdominal pain (1, 7%)

EUS-RFA: Endoscopic ultrasound-guided radiofrequency ablation; RF: radiofrequency; IPMN: intraductal papillary mucinous cystic neoplasm; NET: neuroendocrine tumor; MCN: mucinous cystic neoplasm; SCN: serous cystic neoplasm; PCL: pancreatic cystic lesion; IQR: interquartile range.

45%) or 2 (24 tumors, 60%) sessions of EUS-ELA. Two cases (3.4%) of pancreatitis occurred during 63 ablation procedures. There was no recurrence or progression during a median follow-up period of 42 months (IQR, 39-46 months) in patients who were successfully treated.

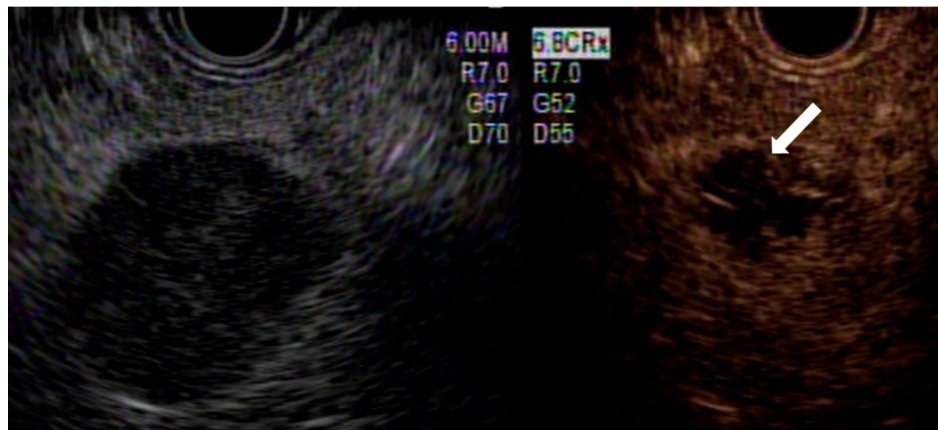


Figure 3. Contrast-enhanced-EUS showing a nonenhanced necrotic portion (arrow) with an enhanced viable tumor. EUS: Endoscopic ultrasound.



Figure 4. Computed tomography (CT) images of a neuroendocrine tumor in the body of pancreas: before treatment, 20-mm hyperenhancing lesion (A); at 3-month follow-up, CT scan showing decreased peripheral rim enhancing lesion (red circle) (B); and at 3-year follow-up, disappearing of ablated lesion (arrow) (C).

Currently, there is no comparative study between EUS-RFA and EUS-guided ethanol ablation for treating benign solid pancreatic tumors. In our experience, these EUS-guided treatments show similar efficacy for ablation of small (< 2 cm) pancreatic tumors. However, some technical issues remain that require further investigation, including the choice of target area and adequate ethanol dosage to achieve successful ablation without causing serious adverse events for EUS-guided ethanol ablation. Furthermore, assuming that the tumor is spherical, ethanol cannot disperse evenly into the tumors for ablation of large tumors (> 2 cm); therefore, treatment effect cannot be predicted. On the other hand, ablation area could be determined by the operator during EUS-RFA. Therefore, for ablation of large tumors, EUS-RFA is preferred to EUS-guided ethanol ablation.

Outcomes of EUS-RFA in pancreas cystic lesion

To date, there have been few studies published on EUS-RFA for treating patients with pancreatic cystic lesions (PCLs). In a prospective study by Pai *et al.*^[19], 6 patients with benign pancreatic neoplasms (PCLs, $n = 6$; and NET, $n = 2$) underwent EUS-RFA using a monopolar radiofrequency catheter (Habib™, EMcision Ltd.). Among these patients, 2 showed complete cyst resolution and 3 had a 48.4% volume reduction without major adverse events. Barthet *et al.*^[13] described their experience over a 12-month period in which 17 patients with PCLs [branch duct intraductal papillary mucinous neoplasm (BD-IPMN), $n = 16$; and

mucinous cystic neoplasm, $n = 1$] underwent EUS-RFA. At the 12-month follow-up, 11 PCLs (65%) had been resolved and one had decreased in diameter by $> 50\%$. In this study, one patient with BD-IPMN experienced jejunal perforation. Aspirating cystic fluid before RFA can avoid having to apply a radiofrequency current into the liquid to ablate the cystic tumors. Oh *et al.*^[20] conducted a retrospective study in 13 patients with microcystic serous cystic neoplasms (SCNs) of honeycomb appearance in whom EUS-RFA was the primary treatment. In this study, radiologic partial response was identified in 8 patients (61.5%), and 1 patient (7.7%) experienced mild abdominal pain. Although the data regarding EUS-RFA for cystic tumors are currently limited, it is a technically feasible, potentially effective, and safe means of managing PCLs.

Outcomes of EUS-RFA in pancreatic cancer

EUS-RFA has been used for treating patients with pancreatic cancer. Song *et al.*^[8] conducted a median of 1.3 sessions of EUS-RFA on 6 patients with unresectable pancreatic cancer. EUS-RFA was successful in all patients, and 2 patients experienced mild abdominal pain without serious adverse events. In a recent study by Scopelliti *et al.*^[9], EUS-RFA combined with systemic chemotherapy was performed in 10 patients with unresectable pancreatic cancer. After tumor ablation, an abdominal computed tomography 30 days post-procedure revealed a delineated hypodense ablated area within the tumor in all patients. Although the role of EUS-RFA on pancreatic cancer is still being investigated, RFA may induce a secondary anticancer immune response by activating tumor-specific T lymphocytes and heat shock protein 70 expression^[21,22]. Thermal ablation could increase blood flow in the ablated tissues^[8]. EUS-RFA could affect post-procedural tumor changes associated with a systemic antitumor immune response, enhancing the systemic chemotherapy effect.

SUMMARY

The recent development of EUS devices has expanded the role of local treatment of EUS in pancreatic tumors. EUS-RFA may be a definite treatment for benign pancreatic tumors. EUS-RFA for pancreatic cancer could reduce tumor size, enhance the chemotherapeutic effect, and improve survival in cases of advanced pancreatic cancer. Given the promising results of previous reports, EUS-RFA can potentially change the clinical management of pancreatic neoplasms. Large-scale, prospective, randomized controlled trials are required to verify the role of EUS-guided ablation in pancreatic neoplasms.

DECLARATIONS

Authors' contributions

Conception and design: Seo DW

Analysis and interpretation of the data: Cho SH, Oh D

Drafting of the article: Cho SH, Oh D

Critical revision of the manuscript for important intellectual content: Seo DW

Supervision: Seo DW

Final approval of the article: Seo DW

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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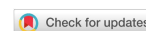
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Editorial

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Forward: A new kind of endoscopists for advanced therapeutic endoscopy

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Since the first endoscopic papillotomy carried out by the physician M. Classen in 1993 (München, Germany, simultaneously with K. Kawai, Kyoto, Japan), numerous non-invasive procedures have been performed by physicians and surgeons with different backgrounds in the biliary-pancreatography field, as well as in all parts of digestive endoscopy. In 2007, natural orifice transluminal endoscopic surgery (NOTES) was more experimental than a promising routine procedure, but it led to the development of devices for full-thickness resection (FTRD), endoscopic submucosal dissection (ESD), and stenting procedures to avoid aggressive palliative surgery. Development of therapeutic endoscopic ultrasonography (EUS) during the last decade has allowed the bile duct access to drainage even when traditional endoscopic retrograde cholangiopancreatography (ERCP) is impossible due to duodenal obstruction. Depending on local teaching organization, all of these therapeutic procedures are performed by either physicians or surgeons. The Chinese Endoscopic Society has proposed the global concept of Endoscopy Society with a special interest for some advanced procedures including in the area called Super Minimal Invasive Surgery (SMIS).

This trend leads to the differentiation as well as reunification of various types of endoscopists. They differentiate when only about 10% of physicians are accredited to perform these very skillful therapeutic procedures, with the other 90% performing gastroscopy and colonoscopy Level 1 (dilation, variceal ligation, polypectomy, etc.). For example, they should not perform ERCP without a very demanding initial training as well as regular practice. ERCP can be carried out in any endoscopy unit, as was done in the early 1980s,



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because it is no less acceptable for patient safety. SMIS, large ESD, full-thickness resection, and stenting procedures can reunify physicians and surgeons in the same crucial but narrow field even if they have different backgrounds.

Consequently, we should organize common training to qualify endoscopists who carry out SMIS and all advanced therapeutic procedures. They should have access to high-level qualification as provided by Research Institute against Digestive Cancer (IRCAD) to avoid malpractice due to inadequate training. When we started ERCP in the 1970s, it was on our own as we did not have a teacher; we were innovators. This is not acceptable in the 21st century. However, common high-level diagnosis endoscopy without minute teaching should not be a pathway for poor surgical colleagues to perform poor diagnosis procedures. With high-resolution endoscopes, imaging-enhanced endoscopy, daily use of classifications for characterization, and diagnosis endoscopy also require a skillful experience and should not be considered as an accessory to a limited surgical practice. For our patient safety, the best is both trained and skillful (surgeons or physicians) endoscopists for high-level therapeutic endoscopy and trained and skillful physicians or surgeons for diagnosis endoscopy.

This new concept needs resources: diagnosis endoscopy requires fewer resources than high-level therapeutic endoscopy, which needs multiple expensive devices. In endoscopy units, nearly all diagnostic endoscopic procedures are carried out in clinics, while, for advanced therapeutic procedures, patients usually have to stay some hours to days in the hospital.

In this special issue focused on biliary and pancreatic diseases, we review all possibilities of advanced diagnosis or therapeutic procedures described by world experts based on clinical practice for the best management of our patients. High-quality endoscopy is mandatory due to its importance in global healthcare.

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The author contributed solely to the article.

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The author declared that there are no conflicts of interest.

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Original Article

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Desarda technique as a valuable alternative for inguinal hernia patients refusing mesh implantation: long-term results fifteen years after a pure tissue repair in 198 patients

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Abstract

Aim: The aim of the study was to retrospectively analyze long-term results of surgical treatment of patients diagnosed with primary inguinal hernia up to 15 years after a Desarda pure tissue repair.

Methods: The study was conducted on a group of adult patients with primary inguinal hernia who underwent elective surgery at our center during 2005-2006. Patients' data and hernia and surgery characteristics were recorded. Incidence of postoperative complications was assessed seven days after surgery. An attempt was made to contact all patients 15 years after the procedure regarding recurrence, possible surgical re-treatment, pain, and satisfaction.

Results: Desarda procedure was performed in 341 patients. Fifteen years after the surgical procedure, a follow-up was successful in 215 (63%) patients, of whom 198 (58.1%) answered all of the questions. In the early perioperative period, minor postoperative complications were found in 5.6% of patients. After 15 years of follow-up, three recurrences were found (1.5%). Recurrences occurred 2, 3, and 5 years after the surgery. All patients expressed their satisfaction with the treatment. Twenty-eight patients (14.4%) reported a rare occurrence of mild pain while performing certain activities. Three patients reported persistent chronic pain (1.5%).



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Conclusion: Surgical repair of primary inguinal hernia using the Desarda technique is a simple, feasible, repeatable procedure, using the patient's own tissues, and with a low learning curve. It seems that the Desarda repair can still be a safe alternative to other non-mesh surgical techniques, especially when the patient refuses the use a synthetic mesh.

Keywords: Inguinal hernia, Desarda technique, pure tissue repair, recurrences, follow-up

INTRODUCTION

Inguinal hernias are a widespread pathology and every fourth man in his life will be affected by this pathology^[1]. Introduction of a polypropylene mesh was a milestone in the hernia repair^[2]. Currently, the most frequently used method is the Lichtenstein repair with the use of an implant strengthening the posterior wall of the inguinal canal^[3]. Techniques based on the use of the patient's own tissues (pure tissue repairs) are currently losing importance due to the possibility of securing hernia with a material of known and durable strength - the polypropylene mesh^[4]. Only the Shouldice method still finds supporters and the long-term results of this method used by experienced surgeons are similar to those of the Lichtenstein method^[5]. A main disadvantage of the Shouldice method is its specific degree of complexity, which means that only some surgeons perform the procedure in a fully correct manner with creation of all four layers of reconstructed tissues^[3,5].

An alternative to both of these methods was proposed in 2001 by an Indian surgeon - Desarda^[6]. He described a method of repair which took into account the biomechanical aspect of the inguinal canal^[6,7]. A bilaterally pedunculated strip of the external oblique aponeurosis is used to strengthen the posterior wall of the inguinal canal [Figure 1]. As a consequence, and contrary to the Shouldice method, tissues of the transverse fascia, which were initially weakened due to a disturbed collagen structure, are not used^[7]. The strip is not separated at both its poles, which that it is included in the dynamic system of forces and stresses occurring in this area. Tension of the abdominal muscles causes the strip of aponeurosis of the external oblique muscle of the abdomen to tighten and expand, simultaneously pressing the posterior wall of the inguinal canal and strengthening the area of the deep ring^[7].

The aim of the study was to retrospectively analyze long-term results of surgical treatment of patients diagnosed with primary inguinal hernia up to 15 years after a Desarda repair surgery. An additional aim of this work is to discuss technical aspects of the presented procedure in detail.

METHODS

Patients

The study was conducted on a group of adult patients with primary inguinal hernia who underwent elective surgery at our center during 2005-2006. All patients operated during this period were qualified for the Desarda repair procedure on the basis of typical indications for the surgical treatment of inguinal hernias, in accordance with current surgical guidelines. Only elective procedures were included in the analysis. Patients with recurrent and strangulated hernias were excluded from the study. It was assumed that patients in whom the external oblique aponeurosis was observed intraoperatively to be significantly thinned or separated into fibers were not eligible for the Desarda surgery, but during the 2-year observation period no patients were excluded for this reason. Surgical procedures were performed by the same team of surgeons. Patients were operated on under regional anesthesia or, in the event of contraindications to this type of anesthesia, under general anesthesia. All patients received thromboprophylaxis 12 h prior to surgery (enoxaparin). All patients were preventively treated with a prophylactic dose of an antibiotic 30 min prior to

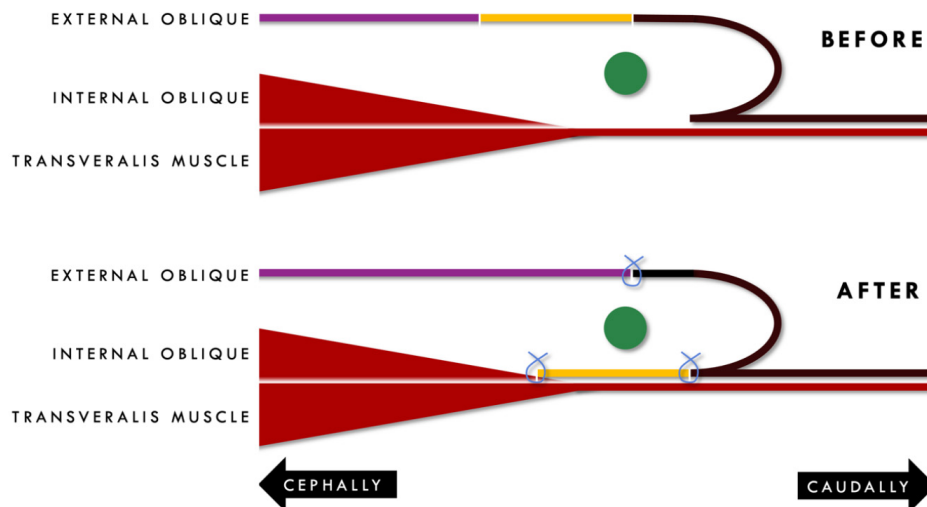


Figure 1. A cross-section scheme of the inguinal canal demonstrating the principles of Desarda repair: a narrow strip of external oblique aponeurosis (yellow) is moved onto a posterior wall of inguinal canal behind spermatic cord (green) and sutured to both the inguinal ligament and the internal oblique (blue). The anterior wall of the inguinal canal is closed with upper/medial flap of the external oblique aponeurosis (purple).

first incision (cefazolin). Patients were enrolled in the study after obtaining their informed consent to participate in the study.

Data and characteristics

Data regarding anthropometric parameters during the surgery (age, sex, and BMI), ASA classification, hernia characteristics (side, location, orifice diameter, and conversion of the hernia type/size to the currently used EHS classification), and duration of the surgical procedure were recorded^[3]. In the immediate postoperative period (up to seven days), incidence of postoperative complications such as hematoma, wound infection, seroma, and testicular swelling was assessed in the operated patients. An attempt was made to contact all patients who underwent Desarda surgery 15 years after the date of the procedure. A team surgeon performed a telephone survey with all available patients. Contacted patients answered four questions from the questionnaire during a telephone interview. The questions concerned recurrence, possible surgical re-treatment of the hernia on the same side, pain at rest and during exercise (according to the Visual Analog Scale), and satisfaction with the treatment result.

Procedure

The skin is incised at a typical site, about 2 cm above and parallel to the inguinal ligament, over a distance of about 5-6 cm. Subcutaneous tissue is incised, paying attention to subcutaneous veins in this area and ligating them. Coagulation of these vessels is avoided as they can be a source of extensive postoperative hematomas. After cutting the Scarpa fascia and dissection of the deep subcutaneous tissue, the aponeurosis of the external oblique abdominal muscle becomes visible. Its condition is visually controlled: thickness, strength, and separation into individual fibers. An apparently thinned structure and the aponeurosis separated into fibers disqualifies from the use of a Desarda method. Sometimes there is a slight rupture in the aponeurosis due to a passage of nerves. These can be used later to create a strip. The superficial inguinal ring is exposed. At its apex, the aponeurosis lamellae are incised parallel to the course of fibers, opening the inguinal canal [Figure 2A] (to clearly visualize the structures of the inguinal canal, the following figures show the anatomical situation of the inguinal region in a female patient). The spermatic cord (or round ligament of the uterus in females) is isolated together with the hernial sac from the external oblique

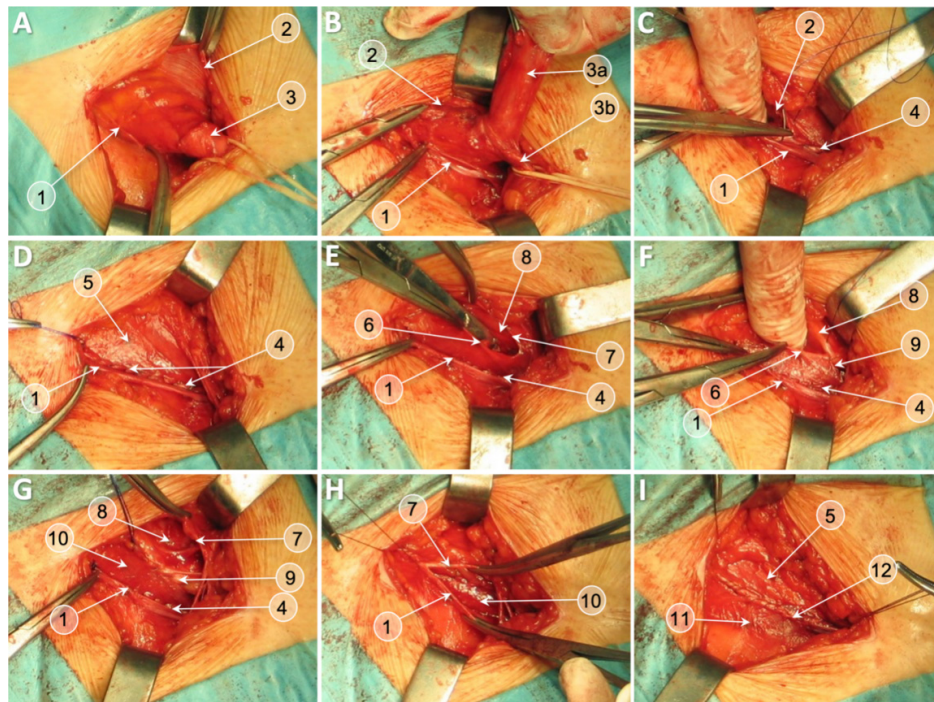


Figure 2. Desarda repair of a groin hernia in female patient (with round ligament resection for better visualization). Anterior wall of inguinal canal is opened (A); hernia sac is dissected (B); lower edge of medial/upper flap of external oblique is sutured to inguinal ligament (C, D); creation of external oblique strip with longitudinal incision (E); the strip is sutured to internal oblique (F, G); and the anterior wall of inguinal canal is closed with external oblique (H, I). Inguinal ligament (1); upper/medial flap of external oblique (2); undissected hernia sac [(3a) dissected hernia sac; and (3b) round ligamentum of uterus] (3); suture line between lower edge of upper/medial flap of external oblique and inguinal ligament (4); external oblique aponeurosis (5); upper edge of a created aponeurotic strip (6); lower edge of the upper flap of remaining incised external aponeurosis (7); internal oblique muscle (8); suture line between upper edge of the strip and internal oblique (9); completed and sutured on both edges aponeurotic strip reinforcing inguinal floor (10); lower flap of initially incised external oblique aponeurosis attached to inguinal ligament (11); and suture line of anterior wall of inguinal canal (12).

aponeurosis. The ilioinguinal, iliohypogastric nerves should be identified, and the genital branch of the genitofemoral nerve should be identified to prevent damage to these structures. The iliohypogastric nerve becomes visible after the separation of the lamina of the internal oblique muscle. The genital nerve can be relatively easily protected by visualizing the veins on the posterior side of the spermatic cord while it is being released from the bottom of the inguinal canal. Avoiding damage to the superficial veins of the spermatic cord protects the genital nerve that runs in this area. The isolated spermatic cord/round ligament is retracted using a rubber drain [Figure 2B]. The hernia sac is managed in the usual manner. After dissecting it to the neck area, the unopened sac is usually pushed into the abdominal cavity. If there are doubts as to the contents of the sac, it should be opened and then sutured and ligated, after checking the content, and the excess is cut off.

In the next stage, the actual hernioplasty is performed using the Desarda technique [Figure 2C and D]. Both flaps of the external oblique aponeurosis (medial/superior and lateral/inferior) are visualized and dissected. Using a continuous single-fiber non-absorbable 2.0 suture (Surgipro®, Tyco), the lower edge of the medial (superior) flap of the external oblique aponeurosis is sutured to the shelving margin of inguinal ligament under the spermatic cord, from the pubic tubercle up to the level of the deep ring. In this way, the deep inguinal ring is recreated, as in the Lichtenstein method - so that it passes freely on the tip of the finger. Excessive constriction of the spermatic cord should be avoided. Then, a 2-2.5 cm wide aponeurosis strip is

made, cutting parallel to the course of fascia fibers, parallel to the inguinal ligament, passing through a possible rupture in the aponeurosis (the place where the iliohypogastric nerve passes). In this way, an aponeurotic strip and a medial flap of the external oblique aponeurosis are formed [Figure 2E]. The medial aponeurotic flap is later used to close the inguinal canal. In the next step, the medial edge of a newly formed lateral aponeurotic strip is secured with a continuous suture to the underlying internal oblique abdominal muscle, using the same material as above [Figure 2F]. In this way, an aponeurotic strip is obtained which is attached to the inguinal ligament on one side and to the internal oblique abdominal muscle on the other side. It extends upward to the distal part of the aponeurosis and downwardly attaches in the region of the upper ramus of the pubic bone [Figure 2G]. This strip strengthens the posterior wall of the inguinal canal, similar to the polypropylene mesh in the Lichtenstein method. The inguinal canal is then closed by suturing the remaining flaps of the fascia with absorbable suture over the spermatic cord/round ligament, typically reconstructing the superficial inguinal ring [Figure 2H and I]. Single stitches on the subcutaneous tissue and the skin complete the procedure.

Statistical analysis

The results obtained during the study were subjected to basic statistical analysis in Microsoft Excel 16.45. Descriptive analysis included the calculation of average values, standard deviations, and proportions. Bivariate analysis was done using Pearson's Chi-square and Fisher's exact test for categorical variables as applicable, and *t* test for continuous variables. A value of $P < 0.05$ was considered a statistically significant difference between the compared groups. All calculations were performed using the Statistica 13.0 licensed statistical analysis software package.

RESULTS

In total, the elective repair according to a Desarda procedure was performed in 341 patients. Fifteen years after the surgical procedure, a phone call follow-up was successful in 215 (63%) patients, of whom 198 (58.1%) answered all of the questions. The characteristics of treated patients and the procedure performed are summarized in Tables 1 and 2. There were no relevant statistical differences between the respondents and the total population of operated on patients. In the early perioperative period, minor postoperative complications were found in 5.6% of patients, all of which resolved spontaneously without additional surgical intervention. After 15 years of follow-up, three recurrences were found, which constituted 1.5% of the patients who answered the questions [Table 3]. Recurrences occurred 2, 3, and 5 years after the treatment, respectively. Nevertheless, all patients expressed their satisfaction with the treatment. Twenty-eight patients (14.4%) reported a rare occurrence of mild pain while performing certain activities, but at the same time they emphasized that this is not a phenomenon that hindered their everyday functioning. Three patients reported persistent chronic pain (1.5%).

DISCUSSION

There is a common consensus that, after Lichtenstein repair procedures, the percentage of observed complications and the number of recurrences are similar for procedures performed by both experienced surgeons and residents^[8]. This is largely the result of a short learning curve characteristic for the procedure. Simplicity of this operation favors the speed of its performance and similar results are achieved both by centers specializing in hernia surgery and small surgical departments. A similar situation seems to be the case with the Desarda surgery. Many common features between these two techniques (i.e., exactly the same anatomical structures need to be dissected in both methods) lead to the conclusion that, as with the Lichtenstein surgery, the Desarda method is lacking a troublesome complexity. Usually, duration of the surgical procedure reflects the scale of difficulties of individual surgical techniques in inguinal hernia repairs. The lack of statistically significant differences in the duration of procedures using the Desarda and

Table 1. Demographic details of all patients and in patients with 15-year follow-up

	All patients	Patients in follow-up	P
Patients, n (%)	341 (100%)	198 (58.1%)	
Age, mean (SD), years	51.9 (14.3)	51.4 (15.1)	0.186
Gender, n (%)			
Male	306 (89.7%)	178 (89.9%)	0.183
Female	35 (11.3%)	20 (11.1%)	0.204
BMI, mean (SD), kg/m ²	25.9 (2.8)	25.8 (2.6)	0.293
ASA			
I	191 (56.0%)	117 (59.1%)	0.072
II	125 (36.7%)	69 (34.8%)	0.108
III	25 (7.3%)	12 (6.1%)	0.116
Smoking, n (%)			
Yes	201 (58.9%)	119 (60.1%)	0.091
No	140 (41.1%)	79 (39.9%)	0.162
Hernia reducibility, n (%)			
Yes	317 (93.0%)	182 (91.9%)	0.137
No	24 (7.0%)	16 (8.1%)	0.171

Table 2. Characteristics of procedures in all patients and in patients with 15-year follow-up

	All patients	Patients in follow-up	P
Procedures, n (%)	341 (100%)	198 (58.1%)	
Anesthesia, n (%)			
Spinal	293 (85.9%)	172 (86.9%)	0.426
General	48 (14.1%)	26 (13.1%)	0.318
Hernia type, n			
Direct (M1/M2/M3)	109 (37/25/47)	63 (24/12/27)	0.227
Indirect (L1/L2/L3)	232 (81/67/84)	135 (45/44/46)	0.108
Surgeon, n (%)			
Resident	88 (25.8%)	48 (24.3%)	0.517
Attending surgeon	253 (74.2%)	150 (75.7%)	0.330
Operation time, mean (SD), min	51.4 (16.2)	52.5 (17.3)	0.199
Nerve resection, n (%)			
Iliohypogastric	74 (21.7%)	45 (22.7%)	0.243
Ilioinguinal	7 (2.1%)	4 (2.1%)	0.302
Genital branch of femoral	0 (0.0%)	0 (0.0%)	

Lichtenstein techniques may indicate their similar degree of difficulty^[8,9]. This distinguishes the Desarda surgery from other low-tension techniques, especially the Shouldice technique, where it has been documented that satisfactory surgical treatment results (recurrence rate below 1%) are obtained only in specialized centers and after operations performed by surgeons experienced in Shouldice technique^[10]. Bracale *et al.*^[11] in a meta-analysis of fourteen randomized controlled trials revealed that Shouldice repair lasted 7 min longer than Lichtenstein repair, while Desarda repair was 6 min shorter than the average Lichtenstein procedure.

Various methods of surgical treatment of inguinal hernia are being compared mainly in terms of recurrence rate. In the analyzed group, 15 years after the surgical procedure, only three recurrences were found. In the literature, the incidence of recurrences after Lichtenstein surgery does not exceed 1%. Kockerling pointed

Table 3. Short- and long-term results of Desarda technique

	Patients in follow-up
	<i>n</i> = 198
Early postoperative complications	11 (5.6%)
Hematoma	5 (2.5%)
Surgical site infection	0 (0%)
Seroma	4 (2.0%)
Scrotal/testicular oedema	2 (1.0%)
Pain (VAS), mean (SD)	0.44 (0.41)
Verbal description of pain, <i>n</i> (%)	
No pain	167 (84.4%)
Mild pain	27 (13.6%)
Moderate pain	4 (2.0%)
Severe pain	0 (0%)
Pain occurrence, <i>n</i> (%)	
No pain	167 (84.4%)
Incidental	28 (14.1%)
Constant pain	3 (1.5%)
Foreign body sensation, <i>n</i> (%)	1 (0.5%)
Loss or change of sensation, <i>n</i> (%)	43 (21.7%)
Patient's full satisfaction, <i>n</i> (%)	
Yes	198 (100%)
No	0 (0%)
Recurrence, <i>n</i> (%)	
Yes	3 (1.5%)
No	195 (98.5%)

out that the recurrence rate after inguinal hernia repairs can still be as high as 11%, of which 43% appear even 10 years after the initial surgery^[12]. There are limited data on the long-term incidence of this complication after the Desarda surgery. Among 1320 inguinal hernia repairs performed by the author of the discussed technique, with at least 7 years of follow-up, only one early recurrence was found, which was a result of an error during surgery^[6,7]. At that time, a direct hernia was identified by mistake, leaving the coexisting indirect hernia unrecognized and, therefore, not properly managed. Szopinski *et al.*^[9] reported two recurrences in a group of 105 patients after Desarda repair (1.9%) which occurred in the weakened area of the posterior wall or internal inguinal ring up to 3 years after the surgery. These results were confirmed by Bracale *et al.*^[11] in a recent systematic review pointing out that the results of Desarda repair have a low recurrence rate similar to the one after the Lichtenstein technique. It seems that these optimistic data will change with popularization of the method and the treatment of a larger number of patients, but results achieved so far should be considered satisfactory.

The undoubted advantage of the Desarda method is the simplicity of its implementation, even by surgeons with little experience in hernia surgery. This brings the learning curve of this technique closer to the way of gaining experience in the Lichtenstein operations. Inguinal hernia repairs are among the most frequently performed operations in surgical departments, especially by young surgeons. It seems that development of hernia techniques should take into account specific needs of this group, i.e., allow the repair to be simple, safe, easy to learn and perform, without the risk of more serious complications during and after the procedure, and with a minimum number of recurrences^[13]. Both the Desarda and Lichtenstein techniques meet the criteria described. Therefore, the Desarda surgery may successfully compete with other open

approach repairs, both with mesh and the use of patient's tissues only.

The Desarda repair may be successfully used in all patients with a normal external oblique aponeurosis. It is especially recommended in cases of surgeries on young slim men with lateral hernias with a narrow internal ring^[14]. The procedure meets all conditions of modern hernia repair: it can be performed on a single-day basis, it is possible to mobilize the patient early, patients may resume professional activities soon after the procedure, only minimal pain is reported, there are no serious complications and recurrences, and a low learning curve is observed^[3,15].

In some cases, this technique is not recommended in patients in whom the external oblique aponeurosis is thinned and separating into fibers. The Lichtenstein surgery is preferred in those cases. Despite certain technical limitations, the Desarda surgery seems to be a certain alternative allowing for hernia repair without the use of mesh implants, especially with regards to the growing number of patients refusing use of mesh. However, there are regions with limited access to modern mesh repairs, mainly in low-income countries, where an effective and safe pure tissue repair may be the only accessible alternative to worldwide recommended mesh repairs^[16]. However, there are many issues that have not been answered yet. Will long-term results of these repairs be similar to, or perhaps surpass, those performed using the Lichtenstein method? Will congenital defects in collagen structure, which are mentioned as the cause of hernia pathogenesis, affect long-term results of this treatment^[17]? The long-term follow-up results presented above supplement the knowledge available in this field. However, the weakness of the study is a low percentage of patients who were available for the long-term follow-up. Taking into account the 15-year follow-up period, it seems that gathering more patients may be impossible, unless the results are entered into dedicated central national medical registers.

There are several limitations to the present study. This study was a retrospective review of a single center's experience. Although it is possible that recurrence results could have been biased from progressive variations, such as alterations in surgeon's experience or other unaccounted for recognized practices, this would be uncertain given surgeon workforce constancy, unchanged surgical practice, and established postoperative pathways throughout the study time phase. Furthermore, patient's sex and age, BMI, smoking habit, and hernia type and size (the major determinants that might influence a recurrence rate) were all similar between the patients included in the follow-up and the entire group of operated on patients. Another possible limitation is the lack of personal examination. Although it was possible to invite some of the patients for a face-to-face interview along with sonography examination, most. Patients were unwilling to undertake a visit, making it unlikely to analyze the outcomes in a large group of patients. A third limitation of our study was that the cohort was not compared with the results in a group treated with a standardized technique (i.e., Lichtenstein repair). This likely reflects the fact that, during the initial implementation of this technique in our center, Desarda repair was a predominant surgical technique used for primary groin hernia repair in the analyzed time period. Despite the retrospective and descriptive character of the study as its drawback, the main intention of the authors was to familiarize the readers with the details of the surgical technique and to present long-term treatment results.

In conclusion, surgical repair of primary inguinal hernia using the Desarda technique is a simple, feasible, repeatable procedure, using the patient's own tissues, and with a low learning curve. The results of treatment of inguinal hernias using this technique allow for a low percentage of recurrences and chronic pain in a long-term follow-up. It seems that the Desarda repair can still be a safe alternative to other non-mesh surgical techniques, especially when the patient refuses the use a synthetic mesh.

DECLARATIONS

Authors' contributions

Conception and design of the study: Mitura K, Skolimowska-Rzewuska M

Data analysis: Mitura K, Skolimowska-Rzewuska M, Wyrzykowska D

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Availability of data and materials

Data supporting these findings are deposited in Siedlce hospital records.

Summarized tables and questionnaires are deposited in Prof. Mitura's academic repositories.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study has been designed and performed in accordance with the Declaration of Helsinki and approved by a Bioethics Committee of the Regional Medical Chamber in Warsaw, Poland (reference number: OIL/KB/12/2005). An informed consent was obtained from all participants.

Consent for publication

Not applicable.

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Technical note

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Ergonomics in robotic surgery: patients' safety and protection during complex procedures

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Abstract

Specific injuries due to poor positioning seen in robotic pelvic surgery include slips, compartment syndrome, facial oedema, injuries on pressure points, and accidental injuries caused by the robotic arms. The use of the vacuum bean-bag positioner, L-bar against the patient's face, and inflated gloves for hand support are simple and effective techniques and should be included in the standard operating policies for robotic surgery. We recommend use of the "L" shaped safety bar against the patient's face to ensure protection against accidental injuries caused by the robotic arms. The anti-slip bean-bag mattress is efficient to prevent slipping; it conforms to the shape of the body for stable positioning and allows extremities to lie in a natural position. Protection of pressure points of hands and elbows can be done with inflated medical gloves placed in the patient's hands. Surgeons, anaesthetists and theatre teams are together responsible for ensuring that safety measures are in place to reduce the risk of these complications.

Keywords: Robotic surgery, ergonomics, intraoperative injuries, positional complications

The last decade has seen some significant technological advances in surgery, leading to improved outcomes; however, as with every new technique there is an associated learning curve, which often entails longer operating times. The patients are usually placed in steep Trendelenburg and tilted positions in pelvic surgery. It is extremely important to ensure that the patients do not slip off the operating table during these



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procedures and to avoid the risk of injuries. Specific injuries which are due to poor positioning include slips, compartment syndrome, facial oedema, and injuries on pressure points, including peripheral neuropathy^[1,2]. Incorrect positioning of the upper and lower limbs on the operating table can lead to peripheral nerve injuries (ulnar, peroneal) and brachial plexopathies, due to compression or stretching^[1].

Robotic surgery adds another element to this complexity by the presence of the insensate robotic arms, and the operator seated at a distance from the operating field. Accidental injuries caused by the robotic arms can result in bruising, burns due to friction of the robotic arms against the body, and facial injuries with potential dislodgement of the endotracheal tube^[3].

The development of a standard operating policy for perioperative care in robotic surgery has been advocated to prevent the above-mentioned complications. Awareness of these potential injuries should be raised and discussed when the patient is consented for the operation, at the team brief meeting and during the robotic procedure^[4]. Surgeons, anaesthetists and theatre teams are all responsible for ensuring that safety measures are in place to reduce the risk of these complications^[5].

The robotic surgical team at our institution has gained experience of over eight years. Working in a multidisciplinary collaboration has enabled us to design a safe pathway for robotic surgery. We have been able to minimise the risk and proceed with safe surgery by following these standardised operating procedures.

We recommend the use of the “L” shaped safety bar above the patient’s face [Figure 1]. This bar is fixed to the operating table and covers the patient’s face and the endotracheal tube, ensuring protection against accidental injuries caused by the contact with the colliding robotic arms.

Various methods have been reported in literature to prevent the slipping of the patient off the table intraoperatively, including straps, shoulder restraints, leg straps and anti-slip mattresses^[2]. We have found that the anti-slip bean-bag mattress is an efficient piece of equipment for preventing slipping [Figure 2]. It is also named surgical vacuum bean bag positioner and is used to prevent the movement of the patient during the Trendelenburg positioning and tilted position of the operating table. Once vacuumed, it conforms to the shape of the body for stable positioning and allows the extremities to lie in a natural position.

Secondly, protection of pressure points at the level of the hands and elbows is extremely important, especially during lengthy procedures, to prevent neuropraxia and compartment syndrome in the hand and forearm^[4]. The use of the inflated medical gloves placed in the hands of the patients is a new technique developed at our institute. The hand and the wrist can rest in a relaxed fashion over these gloves, and the fingers are well supported, too. The thumbs must be kept uppermost. This arrangement can protect the pressure points and prevent neurological injuries [Figure 3].

Lastly, along with these standard procedures, the patient is returned to the supine neutral position for 15 min after every 4 h to avoid compartment syndrome, and calf compression pumps are preferred over the anti-embolism stockings.

These techniques have been used in our institute for the last 10 years in both laparoscopic and robotic surgery. The local incidence of patient slippage and pressure point injuries was 0.5%. This compares favourably low with the overall incidence of 3.6% quoted in robotic rectal cancer operations performed in lithotomy^[5].



Figure 1. Setup of the “L” protective metallic bar *in situ*, along with the anti-slip mattress.

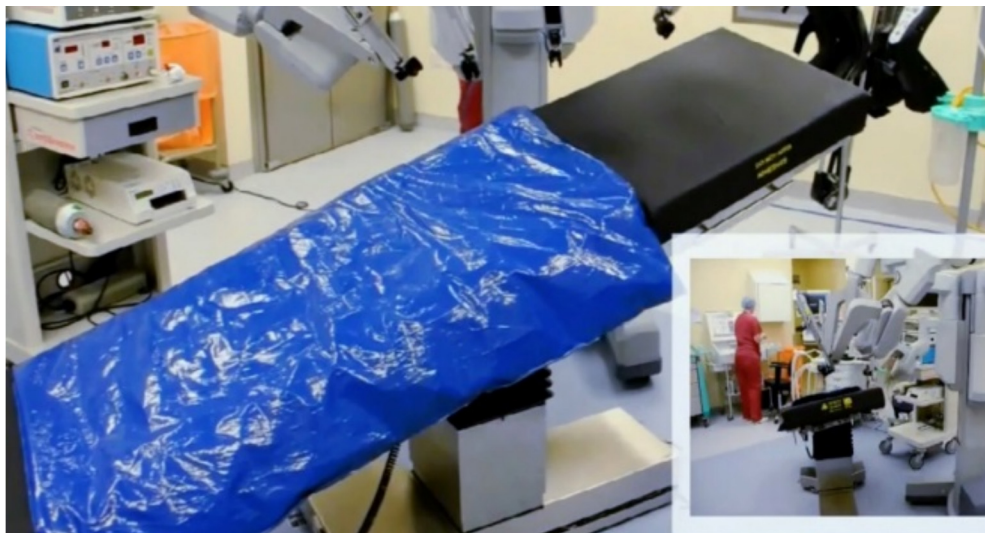


Figure 2. The use of the anti-slip bean-bag mattress.

Every team member involved in the robotic procedure has the responsibility to ensure the patient's safety. Positional complications in surgery although rare, can have serious consequences. As well as causing harm to the patient, there are also potentially increased costs for healthcare and medico-legal implications. Awareness, team training and development of standard operating policies for robotic surgery can reduce the incidence of these perioperative complications^[1,2]. The use of vacuum bean-bag positioner, L-bar against the patient's face, and inflated gloves for hand support are simple and effective techniques that are hereby proposed to be included in the standard operating policies for robotic surgery, to prevent positional complications.



Figure 3. The use of inflated medical gloves to protect the patient's hands and fingers during lengthy surgical procedures.

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Authors' contributions

Wrote and reviewed the manuscript: Stefan SS, Ahmad Y, Khan JS

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Review

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Oncologic outcomes in robot-assisted radical cystectomy: Where do we stand in 2021?

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Abstract

Robot-assisted radical cystectomy is an alternative to the standard open surgical approach and has been increasingly used to surgically treat bladder cancer. Data on oncologic outcomes for the robotic approach have matured, and now intermediate and long-term oncologic outcomes are available. This review focuses on oncologic outcomes of the robotic approach with a focus on recent data and high-quality studies. Based on the current literature available, there are no consistent differences between the robotic and open approaches with respect to positive margin rates, lymph node yields, recurrence patterns, or recurrence free, cancer-specific, and overall survival. If oncologic surgical principles are adhered to, excellent oncologic outcomes are achievable with the robotic approach.

Keywords: Urinary bladder neoplasms, radical cystectomy, robotic radical cystectomy, oncologic outcomes, robotics, recurrence, survival

INTRODUCTION

Radical cystectomy and pelvic lymph node dissection is standard of care for surgically eligible patients with non-metastatic muscle-invasive bladder cancer, and is a preferred treatment for select patients with high risk of non-muscle invasive disease^[1,2]. While open radical cystectomy has been the recognized gold standard for years, robot-assisted radical cystectomy (RARC) has become increasingly popular. Initially



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described by Menon *et al.*^[3] in 2003, utilization of RARC increased from 0.7% in 2002 to 18.5% in 2012 in the United States^[4]. Advantages of the robotic approach relative to open radical cystectomy (ORC) include reduced blood loss, favorable transfusion rate and shorter length of stay^[5].

Here, we review pertinent oncologic outcomes in the current RARC literature. We queried the PubMed electronic database in January 2021 for studies that report on oncologic outcomes for RARC. An emphasis was placed on randomized controlled trials, as well as contemporary comparative open approach cohorts, large single institution surgical series, multi-center initiatives and systematic reviews. A list of the major studies considered in this review is found in [Table 1](#).

NODAL YIELD

Lower nodal yield and positive surgical margin status are independently associated with worse OS after adjustment for neoadjuvant chemotherapy and pathologic factors. In fact, nodal yields of 10-14 have been proposed as a marker of surgical quality^[33]. Professional guidelines and best practice statements are less quantitatively prescriptive^[1,34], as patient, clinical and pathologic factors can influence lymph node yield. In a 2015 systematic review, Yuh *et al.*^[35] assessed 105 papers and found that median yield for a robotic approach was 19 lymph nodes (range: 3-55) with cumulative analyses finding no difference *vs.* ORC. Nodal yields are directly related to the surgical dissection template chosen, whether standard or extended. Among robotic surgeons, high volume surgeons and institutional volume were independently associated with performance of extended template dissections^[36].

Several RCTs have found comparable nodal yields between RARC and ORC [[Table 2](#)]. Nix *et al.*^[11] found mean LN yields of 19 *vs.* 18 in RARC *vs.* ORC ($P = 0.51$) using a standard dissection template. In the largest clinical trial, RAZOR investigators found similar median lymph node yields of 23.3 for RARC with 51% utilizing an extended template, and 25.7 for ORC with 55% utilizing an extended template ($P = 0.13$)^[6]. Other smaller RCTs reported similar findings^[8,9]. Several recent meta-analyses did not assess nodal yield^[37,38].

Considering the abundance of data, adequate lymph node yields are achievable via robotic platforms, including extended and super extended templates. Maintenance of oncologic principles including performance of a meticulous dissection within pre-defined anatomic boundaries of a template appears to be more important than surgical approach.

POSITIVE MARGIN RATE

Positive surgical margin (PSM) rate is a measure of local disease burden, an independent predictor of survival, and can be a measure of surgical quality^[33,39,40]. Early criticism of minimally invasive approaches was that there was risk of higher positive margin rates in locally advanced tumors, as evidenced by a single non-controlled, non-comparative retrospective study^[32]. It was theorized that the lack of tactile feedback and learning curve was potential explanations^[35,41].

These early criticisms have largely been refuted. A systematic review showed that PSM rate was low in pT2 disease (< 1.5%) and 0%-25% in pT3 disease or higher, without any significant difference between ORC and RARC in a cumulative analysis of 17 studies^[35]. Interestingly, PSM did not appear to decrease with sequential case numbers or institutional volume^[32], a finding that may reflect surgeons' willingness to take on more difficult cases with experience^[35]. As a result of these early robotic data and historical open cystectomy series, acceptable PSM rates for robotic surgeons were proposed as < 3% for pT2, < 10% for pT3, < 25% for pT4 and < 7% overall^[34,40].

Table 1. Selected studies evaluating oncologic outcomes after robot-assisted radical cystectomy

Ref.	Year	Comparison	Study design	Setting	Primary outcome	Pertinent secondary outcome(s)
Comparative studies, randomized						
RAZOR trial, multiple authors ^[6,7]	2020, 2018	ORC vs. RARC	RCT	Multi center	2-year PFS	TTR, PFS, OS
CORAL trial, Khan <i>et al.</i> ^[8]	2020	ORC vs. RARC vs. LRC	RCT	Single center	5-year RFS, CSS, OS	Surgical margin, recurrence patterns
Bochner <i>et al.</i> ^[9]	2018	ORC vs. RARC	RCT	Single center	90-day complication	RFS, CSS, OS, recurrence patterns
Parekh <i>et al.</i> ^[10]	2012	ORC vs. RARC	RCT	Single center	Surgical margin Total lymph node yield	Quality of life Functional recovery
Nix <i>et al.</i> ^[11]	2010	ORC vs. RARC	RCT	Single center	Lymph node yield	Demographics, perioperative, pathologic results, narcotic use
Comparative studies, non-randomized						
RACE study, Wijburg <i>et al.</i> ^[12]	2021	ORC vs. RARC	Prospective	Multi center	90-day complication	HRQOL, complications, clinical outcomes including surgical margin
Asil <i>et al.</i> ^[13]	2021	ORC vs. RARC	Retrospective	Multi center	Intraoperative and postoperative endpoints	Surgical margin, lymph node yield
Ip <i>et al.</i> ^[14]	2020	ORC vs. RARC	Retrospective	Single center	RFS, OS	Perioperative and pathologic outcomes
Zhang <i>et al.</i> ^[15]	2020	ORC vs. RARC	Retrospective	Single center	Perioperative outcomes, complications	Pathologic outcomes, overall survival
Faraj <i>et al.</i> ^[16]	2019	ORC vs. RARC	Retrospective	Single center	RFS, OS	Recurrence patterns, predictors of primary outcome
Moschini <i>et al.</i> ^[17]	2019	ORC vs. RARC	Retrospective	Multicenter	Surgical margin status	Predictors of surgical margin status
Simone <i>et al.</i> ^[18]	2018	ORC vs. RARC, ICUD only	Retrospective	Single center	RFS, CSS, OS	Complications, perioperative and pathologic outcomes
Hanna <i>et al.</i> ^[19]	2018	ORC vs. RARC	Retrospective	Population registry	Intraoperative and postoperative endpoints	Descriptors and predictors of robotic surgical approach
Gandagli <i>et al.</i> ^[20]	2016	ORC vs. RARC	Retrospective	Multi center	RFS, CSS, OS	Complications, perioperative and pathologic outcomes, recurrence
Tan <i>et al.</i> ^[21]	2016	ORC vs. RARC	Retrospective	Single center	RFS	Recurrence patterns, CSS, OS
Matulewicz <i>et al.</i> ^[22]	2016	ORC vs. RARC	Retrospective	Population registry	Surgical margin status, lymph node yield	Primary outcome variables as predictors of survival
Nguyen <i>et al.</i> ^[23]	2015	ORC vs. RARC	Retrospective	Single center	RFS	Recurrence patterns at 2 years
Atmaca <i>et al.</i> ^[24]	2015	ORC vs. RARC, ICUD only	Retrospective	Single center	Demographics, functional, intraoperative outcomes	Surgical margin, lymph node yield
Non-comparative studies						
IRCC, Elsayed <i>et al.</i> ^[25]	2021	RARC only	Retrospective	Multicenter	RFS, LRFS, DMFS, OS	Recurrence patterns, predictors of recurrent free survival
Brassetti <i>et al.</i> ^[26]	2020	RARC, ICUD only	Retrospective	Multicenter	RFS, CSS, OS	Surgical margin, lymph node yield, predictors of survival
IRCC, Hussein <i>et al.</i> ^[27]	2019	RARC only	Retrospective	Multicenter	10-year RFS, CSS, OS	Surgical margin, lymph node yield, predictors of survival

IRCC, Hussein <i>et al.</i> ^[28]	2017	RARC only	Retrospective	Multicenter	Incidence of early oncologic failure (any disease relapse < 3 mo s/p RARC)	Recurrence patterns, adherence to oncologic principles, predictors of early oncologic failure
ERUS, Collins <i>et al.</i> ^[29]	2017	RARC, ICUD only	Retrospective	Multicenter	RFS	Recurrence patterns
IRCC, Raza <i>et al.</i> ^[30]	2015	RARC only	Retrospective	Multicenter	5-year RFS, CSS, OS	Surgical margin, lymph node yield, predictors of survival
IRCC, Hellenthal <i>et al.</i> ^[31]	2011	RARC only	Retrospective	Multicenter	Proportion of RARC w/lymphadenectomy performed	Lymph node yield, predictors of lymphadenectomy performance
IRCC, Hellenthal <i>et al.</i> ^[32]	2010	RARC only	Retrospective	Multicenter	Surgical margin status	Predictors of surgical margin status

RAZOR: Randomized open vs. robotic cystectomy; ORC: open radical cystectomy; RARC: robotic assisted radical cystectomy; RCT: randomized controlled trial; TTR: time to recurrence; RFS: recurrence free survival; PFS: progression free survival; CSS: cancer specific survival; OS: overall survival; CORAL: controlled three-arm trial of Open, Robotic, and laparoscopic radical cystectomy; RACE: radical cystectomy evaluation; HRQOL: health-related quality of life; IRCC: International Robotic Cystectomy consortium; LRFS: local recurrence free survival; DMFS: distant metastasis free survival; ICUD: intracorporeal urinary diversion; ERUS: European Association of Urology Robotic Urology Section; LRC: laparoscopic radical cystectomy.

Since then, multiple RCTs and retrospective comparative studies offer additional insight that robotic cystectomy can meet these standards of surgical quality. The RAZOR trial showed overall PSM rates of 5% (ORC) *vs.* 6% (RARC), $P = 0.6$ without any difference in pathologic stage between the groups. Of those with PSMs, 7/9 (78%) in RARC and 5/7 (71%) in ORC were T3 or above^[6]. Two smaller RCTs also found no difference in PSM rate between open and robotic approaches^[8,9]. A meta-analysis compiling 541 patients from RCTs showed no difference in PSM rates between RARC and ORC (RR = 1.2; 95%CI: 0.6-2.4)^[37]. Additionally, one non-randomized comparative study found significantly increased PSM rate for ORC (18%) *vs.* RARC (6%) in an inversed probability weighted population despite similar pathologic staging, though when further specified by site of positive margin these results were not significantly different^[12]. Multiple other non-randomized comparative studies have not found significant differences in PSM rate by approach^[13-17,19,20,22-24].

Collectively, the above data suggest favorable PSM rates are achievable via the robotic platform and are in alignment with standards of surgical quality set forth by best practices statements^[34]. Regardless of surgical approach, the largest determinant of PSM rates is local disease stage.

RECURRENCE PATTERNS

Recurrence of bladder cancer after radical cystectomy is dependent on tumor and nodal stage, and ranges from 20% to 30% in pT2 disease, 40% for pT3, > 50% for pT4 and approximately 70% in pN1 disease or greater^[42]. Other independent predictors of tumor recurrence include lymphovascular invasion and positive soft tissue margins^[43]. Recurrences generally occur within the first 2-3 years and predict worse overall survival (OS)^[44].

Recurrence is generally classified as local, often referring to the cystectomy bed and within the pelvic lymph node template, or distant. Atypical patterns in MIS generally refer to peritoneal carcinomatosis, abdominal wall/port site metastases and extra pelvic lymph node recurrences, which have been described but are rare. In fact, a systematic review of 1094 studies found only 5 that reported port site metastasis^[45]. Proposed contributors of atypical recurrence patterns in MIS include depressive local immunologic factors and/or enhanced tumor dissemination related to pneumoperitoneum, breach of oncologic operative principles,

Table 2. Oncologic outcomes from selected studies after robot-assisted radical cystectomy

Ref. and study acronym	Year	Surgical approach	Cases, (n)	PSM, n (%)	Lymph node yield, mean (SD) or median (IQR or range)	RFS	CSS	OS
Comparative studies, randomized								
RAZOR trial, multiple authors ^[6,7]	2020, 2018	ORC	152	7 (5)	25.7 (SD 14.5)	65%, 3 yr	nr	69%, 3 yr
		RARC	150	9 (6)	23.3 (SD 12.5)	68%, 3 yr	nr	74%, 3 yr
CORAL trial, Khan <i>et al.</i> ^[8]	2020	ORC	20	2 (10)	18.5 (IQR 14-25)	60%, 5 yr	64%, 5 yr	55%, 5 yr
		RARC	20	3 (15)	14.5 (IQR 11-21)	58%, 5 yr	68%, 5 yr	65%, 5 yr
		LRC	19	1 (5)	15.5 (IQR 12-22)	71%, 5 yr	69%, 5 yr	61%, 5 yr
Bochner <i>et al.</i> ^[9]	2018	ORC	58	3 (5)	29 (IQR 22-38)	59%, 5 yr	80%, 5 yr [#]	65%, 5 yr [#]
		RARC	60	2 (3)	31 (IQR 23-37)	64%, 5 yr	75%, 5 yr [#]	65%, 5 yr [#]
Parekh <i>et al.</i> ^[10]	2012	ORC	20	1 (5)	23 (IQR 15-28)	nr	nr	nr
		RARC	20	1 (5)	11 (IQR 9-22)	nr	nr	nr
Nix <i>et al.</i> ^[11]	2010	ORC	20	0 (0)	18 (range 8-30)	nr	nr	nr
		RARC	21	0 (0)	19 (range 12-30)	nr	nr	nr
Comparative studies, non-randomized								
RACE study, Wijburg <i>et al.</i> ^[12]	2021	ORC	168	nr (18)*	13 (IQR 9-18)	75%, 1 yr	nr	nr
		RARC	180	nr (6)	15 (IQR 11-21)	76%, 1 yr	nr	nr
Asil <i>et al.</i> ^[13]	2021	ORC	31	1 (3)	22 (nr)	nr	nr	nr
		RARC	61	9 (15)	Range 22-25	nr	nr	nr
Ip <i>et al.</i> ^[14]	2020	ORC	159	23 (14)	20 (SD 14)*	75%, 5 yr [#]	nr	65%, 5 yr [#]
		RARC	73	8 (11)	12 (SD 8)	80 %, 5 yr [#]	nr	70%, 5 yr [#]
Zhang <i>et al.</i> ^[15]	2020	ORC	272	22 (8)	nr	nr	nr	55%, 5 yr
		RARC	676	34 (5)	nr	nr	nr	58%, 5 yr
Faraj <i>et al.</i> ^[16]	2019	ORC	278	15 (5)	12 (IQR 9-18)*	63%, 10 yr	nr	46%, 10 yr
		RARC	203	7 (3)	18 (IQR 14-24)	70%, 10 yr	nr	40%, 10 yr
Moschini <i>et al.</i> ^[17]	2019	ORC	1666	160 (10)	16 (10-24)	nr	nr	nr
		RARC	870	112 (13)	18 (12-25)	nr	nr	nr
Simone <i>et al.</i> ^[18]	2018	RARC, ICUD only	64	0 (0)	33.4 (SD 12.3)	79%, 4 yr	85%, 4 yr	82%, 4 yr
		ORC	46	0 (0)	31.3 (SD 14.6)	73%, 4 yr	86%, 4 yr	80%, 4 yr
Hanna <i>et al.</i> ^[19]	2018	ORC	7513	(10.7)	12 (IQR 7-20)*	nr	nr	nr
		RARC	2048	(9.3)	17 (IQR 10-25)	nr	nr	nr
Gandagli <i>et al.</i> ^[20]	2016	ORC	230	31 (13)	13 (IQR 9-17)	57%, 5 yr	62%, 5 yr	58%, 5 yr
		RARC	138	12 (9)	12 (IQR 8-17)	54%, 5 yr	74%, 5 yr	59%, 5 yr
Tan <i>et al.</i> ^[21]	2016	ORC	90	17 (19)*	12.6 (SD 10.9)	70%, 2 yr	81%, 2 yr	74%, 2 yr

Matulewicz <i>et al.</i> ^[22]	2016	RARC	94	6 (8)	14.9 (SD 10.0)	79%, 2 yr	84%, 2 yr	84%, 2 yr
		ORC	9639	(13)	11 (IQR 5-19)*	nr	nr	nr
		RARC	2397	(11)	16 (IQR 9-25)	nr	nr	nr
Nguyen <i>et al.</i> ^[23]	2015	ORC	120	15 (13)*	20 (IQR 11-27)	60%, 5 yr [#]	nr	nr
		RARC	263	16 (6)	21 (IQR 13-28)	70%, 5 yr [#]	nr	nr
Atmaca <i>et al.</i> ^[24]	2015	ORC	42	1 (2)	17 (SD 13.5)	nr	nr	nr
		RARC, ICUD only	32	2 (6)	25 (SD 9.7)	nr	nr	nr
Non-comparative studies								
IRCC, Elsayed <i>et al.</i> ^[25]	2021	RARC only	2107	nr	nr	66%, 5 yr	nr	60%, 5 yr
Brasetti <i>et al.</i> ^[26]	2020	RARC, ICUD only	113	9 (8)	36 (IQR 28-45)	58%, 5 yr	61%, 5 yr	54%, 5 yr
IRCC, Hussein <i>et al.</i> ^[27]	2019	RARC only	446	30 (7)	14 (IQR 9-22)	59%, 10 yr	65%, 10 yr	35%, 10 yr
ERUS, Collins <i>et al.</i> ^[29]	2017	RARC, ICUD only	717	34 (4)	18 (IQR 13-25)	75%, 2 yr		
IRCC, Raza <i>et al.</i> ^[30]	2015	RARC only	702	55 (8)	16 (IQR 10-24)	67%, 5 yr	75%, 5 yr	50%, 5 yr
IRCC, Hellenthal, <i>et al.</i> ^[31]	2011	RARC only	527	nr	17.8 (range 0-68)	nr	nr	nr
IRCC, Hellenthal, <i>et al.</i> ^[32]	2010	RARC only	513	35 (6.8)	nr	nr	nr	nr

[#]Visual estimate based on Kaplan Meier curves provided in paper (specific numbers not provided by reference in text). * $P < 0.05$. PSM: Positive surgical margin; SD: standard deviation; IQR: interquartile range; RFS: recurrence free survival; CSS: cancer-specific survival; OS: overall survival; ORC: open radical cystectomy; RARC: robotic assisted radical cystectomy; LRC: laparoscopic radical cystectomy; nr: not reported; ICUD: intracorporeal urinary diversion; RAZOR: randomized open vs. robotic cystectomy; CORAL: controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy; RACE: radical cystectomy evaluation; IRCC: International Robotic Cystectomy Consortium; ERUS: European Association of Urology Robotic Urology Section.

or variant lymphatic dissemination related to robotic technique^[23].

Nguyen *et al.*^[23] reported atypical patterns of recurrence in a non-randomized single center comparative study of ORC vs. RARC, including higher incidence of peritoneal carcinomatosis (21% vs. 8%) and extra pelvic lymph node (23% vs. 15%) [Table 3]. However, the denominator of these estimated proportions was distant recurrences and not overall recurrence, as is typically reported. It was additionally notable that distant recurrences were not significantly different between the two approaches, and the authors noted that selection bias may have contributed to these findings. The same group published a follow up study consisting of 310 patients and found that predictors of distant recurrences, peritoneal carcinomatosis and extra pelvic lymph node metastases did not significantly differ and concluded that tumor biology is likely the chief influencer of atypical recurrence, not surgical approach^[46]. Bochner *et al.*^[9] later found that there was variation in location of recurrence and that RARC resulted in greater numbers of recurrences in the abdomen and pelvis. However, this only achieved significance when pooled and stratification of abdominal recurrences as separate from distant and local recurrences is controversial and of unclear clinical significance^[47]. Notably, the study was not powered to determine differences in patterns of recurrence.

Table 3. Recurrence patterns from selected studies

Ref.	Year	Surgical approach	Cases (n)	Local recurrence ^a , n (%)	Distant recurrence ^b , n (%)	Atypical recurrence ^c			Significantly different?	Comments
						Peritoneal carcinomatosis, n (%)	Abdominal wall/port site, n (%)	Extra pelvic lymph nodes, n (%)		
Comparative studies, randomized										
RAZOR trial, multiple authors ^[6,7]	2020, 2018	ORC	152	3 (2.0)	25 (16.4)	1 (0.7)	1 (0.7)	9 (5.9)	No	Largest RCT to date
CORAL trial, Khan et al. ^[8]	2020	RARC	150	6 (4.0)	22 (14.7)	2 (1.3)	0	9 (6.0)	No	Small sample size. Distant recurrences reported in aggregate only, not shown here
		ORC	20	3 (15.0)	nr	nr	nr	nr		
		RARC	20	3 (15.0)	nr	nr	nr	nr		
		LRC	19	3 (15.7)	nr	nr	nr	nr		
Bochner et al. ^[9]	2018	ORC	58	5 (8.6)	27 (46.6)	2 (3.4)	0	10 (17.2)	No ^d	Not powered to detect differences in recurrence patterns
		RARC	60	17 (28.3)	20 (33.0)	2 (3.3)	5 (8.3)	5 (8.3)		
Comparative studies, non-randomized										
Faraj et al. ^[16]	2019	ORC	278	19 (7)	64 (23)	5 (1.8)	0	11 (4.0)	No	Large single institutional study
		RARC	203	12 (6)	40 (20)	4 (2.0)	0	4 (2.0)		
Tan et al. ^[21]	2016	ORC	90	17 (19)	25 (28)	3 (3)	1 (1)	2 (2)	No	Intracorporeal diversions in all robotic cases
		RARC	94	11 (12)	8 (9)	2 (2)	1 (1)	3 (3)		
Nguyen et al. ^[23]	2015	ORC	79	15/65 (23)	26/73 (36)	2/26 (8)	nr	4/26 (15)	Yes	Denominator is distant recurrence, as listed in the reference
		RARC	158	24/136 (18)	43/147 (29)	9/43 (21)	nr	10/43 (23)		
Non-comparative studies										
IRCC, Elsayed et al. ^[25]	2021	RARC only	2107	241 (11)	382 (18)	26 (1.2)	25 (1.2)	109 (5.2)	n/a	RARC not associated with different patterns or higher recurrence relative to historic ORC series
IRCC, Hussein et al. ^[27]	2019	RARC only	446	69 (15)	97 (22)	6 (1)	5 (1)	21 (5)	n/a	Analysis restricted to patients with > 10 years follow up
Collins et al. ^[29]	2017	RARC, ICUD only	717	78 (10.7)	128 (17.8)	5 (0.7)	2 (0.3)	47 (6.6)	n/a	Totally intracorporeal urinary diversion cohort

^aLocal recurrence defined as any recurrence in the cystectomy bed or lymph node dissection template. ^bDistant recurrence defined as any recurrence which is not local or atypical. ^cThough sometimes reported in the referenced studies as a subset of distant recurrences, atypical recurrences reported here are mutually exclusive of local and distant recurrence. ^dThe difference in local recurrence rates did not meet conventional levels of significance (sHR = 0.36; 95%CI: 0.11-1.12, *P* = 0.077). Similarly, the difference in the rate of abdominal recurrence did not reach statistical significance (sHR = 0.38; 95%CI: 0.07-1.96; *P* = 0.2). However, when the pelvic and abdominal recurrences were combined into a single group representing local/regional recurrence, the ORC group showed significantly less local/regional recurrence compared to RARC (sHR = 0.34; 95%CI: 0.12-0.93; *P* = 0.035). RAZOR: randomized open vs. robotic cystectomy; ORC: open radical cystectomy; RARC: robotic assisted radical cystectomy; RCT: randomized controlled trial; CORAL: controlled three-arm trial of open, robotic, and laparoscopic radical cystectomy; IRCC: International Robotic Cystectomy Consortium; ICUD: intracorporeal urinary diversion; nr: not reported.

Multiple studies have since demonstrated that recurrence patterns do not differ by surgical approach. The RAZOR trial found no significant difference between ORC and RARC in recurrence patterns and showed low overall local recurrence rates (2% vs. 4%). Rare atypical recurrences were also observed in the ORC arm and did not differ between approaches^[7]. A large non-randomized single center comparative study from Mayo Clinic in Arizona showed similar rates of local, distant and rare atypical recurrences^[16]. An institutional report of ~180 cases, 90 of which were robotic with intracorporeal diversion, showed a low rate of atypical recurrences with no difference between surgical approaches^[21]. An IRCC study of 2107 pts showed slightly higher local recurrence (11%, citing a greater percentage of extravesical disease and variant histology in their cohort) with atypical recurrence patterns similar to ORC series and those of the RAZOR trial^[7,25]. A separate IRCC analysis found that tumor factors rather than those related to surgical approach were predictive of early recurrence after cystectomy and also showed that surgeons in their cohort reported a very low rate of divergence from oncologic principles^[28]. Lastly, a large multi-institutional robotic cystectomy and totally intracorporeal urinary diversion cohort from the EAU Robotic Urology Section Scientific Working Group found that early recurrence rates and patterns appeared comparable to open series^[29].

If oncologic principles are followed, these aggregate data suggest that atypical recurrence is exceedingly rare and are more likely reflective of tumor biology than surgical approach.

SURVIVAL OUTCOMES

The primary measure of treatment efficacy in radical cystectomy is survival, including recurrence-free, cancer-specific and overall survival^[1]. Though reported here for reference, we would discourage direct comparison across studies as there is significant heterogeneity with respect to cancer variables (e.g., receipt of neoadjuvant chemotherapy, disease stage, and tumor histopathology), patient demographic and clinical characteristics, surgeon and institutional factors including intra-operative practices and post-operative follow up protocols, adjuvant therapies and length of follow up. This heterogeneity is reflected by a 2015 systematic review of mostly retrospective studies which demonstrated a wide range of 5-year survival estimates of DFS, CSS and OS between 53%-74%, 66%-80% and 39%-66%, respectively^[35].

Several contemporary comparative studies do offer additional limited insight, though we are only aware of 3 RCTs that report survival outcomes. RAZOR is the largest RCT reporting survival outcomes at approximately 150 patients in each arm and reports 3 year outcomes^[7]. RARC was similar compared with ORC in RFS (68% vs. 65%, $P = 0.6$) and OS (74% vs. 69%, $P = 0.3$). Bochner *et al.*^[9] found that a median follow up of 4.9 years, no differences were observed in recurrence [hazard ratio (HR) = 1.27; 95%CI: 0.69-2.36; $P = 0.4$], cancer-specific survival ($P = 0.4$), or overall survival ($P = 0.8$). However, the authors cautioned that their study was not powered to assess survival outcomes. A meta-analysis with pooled data from these two studies found that RARC and ORC may result in similar time to recurrence (HR = 1.1; 95%CI: 0.8-1.4), but the evidence of certainty was low^[37]. More recently, the CORAL study reported 5-year RFS, CSS, OS as well and found no differences in surgical approaches comparing open vs. robotic vs. laparoscopic approaches^[8]. However, their study was limited by low sample size as only 20 patients were included in each arm and included high-risk non-muscle invasive bladder cancer.

Though lacking the rigor of a controlled trial, long-term oncologic outcomes from several robotic cohorts have recently become available. Faraj *et al.*^[16] reported their 10 year survival outcomes in a single institution retrospective comparative study and found that RFS and OS were similar between ORC and RARC approaches (63% vs. 70%, $P = 0.14$ and 46% vs. 40%, $P = 0.47$ respectively). The cohorts were similar in cancer characteristics, patient demographics and clinical factors as well as intra operative practices.

Retrospective non-comparative results from the IRCC on patients with long-term follow up show RFS, CSS and OS at 10 years were 59%, 65% and 35%, consistent with historical ORC and MIS cohorts^[27]. Not surprisingly, in multivariable models, they found that survival was associated with age, positive margins, tumor/nodal stage, and adjuvant treatments. Similar results are described in a multicenter study among RARC patients with totally intracorporeal urinary diversion^[26]. A single institutional comparative study also showed similar survival in a totally intracorporeal urinary diversion robotic cohort when compared with ORC^[18].

Matured, long-term survival data from randomized controlled studies, including RAZOR, are further anticipated. Early and intermediate survival outcomes between RARC and ORC appear to be similar. Since no consistent difference in PSM rates or recurrence patterns have been found in the literature, we expect long-term survival differences to be driven largely by factors related to disease aggressiveness including stage and need for adjuvant therapies, rather than surgical approach.

FUTURE PERSPECTIVES

Nearly 20 years after the robotic approach to radical cystectomy was described^[3], RARC remains an effective and minimally invasive option for patients undergoing cystectomy that can achieve oncologic outcomes that are comparable to the gold standard open approach. Evidence-based consensus and best practices on RARC are available^[34].

There are no absolute contraindications to the robotic approach, but an early learning curve is recognized and several challenging case scenarios (e.g., large bulky tumors, history of pelvic radiation) should be preferentially managed by experienced robotic surgeons. RARC can be safely utilized in the octogenarian^[48], and oncologic outcomes are excellent in sex-sparing techniques in the female patient^[49] as well as male patient^[50]. Excellent pathologic outcomes have been described for aggressive histopathological variants which are known to present with higher tumor stage^[51]. The usage of the robotic approach to cystectomy will continue to increase as urologic surgeons become more experienced and comfortable with the platform and education becomes more commonplace in residency training programs^[4].

Though the current evidence is well-supported, it is limited by the lack of large, randomized controlled trials. We eagerly anticipate more mature, high-quality data comparing oncologic outcomes of open and robotic cystectomy. Robot-assisted radical cystectomy with intracorporeal urinary diversion *vs.* open radical cystectomy (iROC) is a multicenter prospective RCT in England randomizing 320 patients to iRARC or ORC. Accrual finished in February 2020, and oncologic outcomes of interest include atypical recurrence patterns, survival, as well as outcomes related to surgeon fatigue, cost-effectiveness and patient quality of life^[52].

CONCLUSION

Surgical quality indicators, including lymph node yield and positive surgical margin rate, are comparable between ORC and RARC. Despite an early case series of atypical recurrence patterns, contemporary comparative studies, including the largest randomized controlled trial, as well as a multi-institutional retrospective robotic cohort of > 2000 consecutive patients, show this is a rare occurrence and not associated with surgical approach. Survival outcomes appear to be similar as well, including long term survival from several comparative and non-comparative reports. Ultimately, surgeon comfort with the selected approach and adherence to oncologic principles is more important than the approach itself.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data acquisition and interpretation: Miller BL, Lau CS, Pachorek M, Yuh B, Sam AP

Performed data acquisition, as well as provided administrative, technical, and material support: Miller BL, Lau CS, Pachorek M

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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Review

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How to access the common bile duct

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Abstract

Biliary access is a prerequisite to all endoscopic interventions in the biliary tract. Successful cannulation of the papilla of Vater is the predominant challenge for the majority of endoscopists training in endoscopic retrograde cholangiopancreatography (ERCP), and the skills required for success differ substantially from those of regular luminal endoscopy. This paper reviews some of the key elements to successful biliary cannulation, a range of options for problem-solving when cannulation is difficult, and some tips and tricks in select special situations as well. The techniques are described, and available evidence is reviewed.

Keywords: Endoscopy, ERCP, endoscopic interventions, cannulation, papilla of Vater

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has since its inception 50 years ago been considered one of the most sophisticated, challenging and risky endoscopy procedures. Although recent advances in available accessories and imaging have reduced risks, it remains a complex procedure, requiring skills and training different from luminal endoscopy, from where most endoscopists arrive. It also requires access to - and understanding of - cross-sectional imaging and ductal anatomy.

The procedure may include a number of different elements, but common to all is the necessity to cannulate the papilla and achieve deep access to the desired duct, most often the bile duct. Successful cannulation of



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the native papilla is usually the primary obstacle of novice endoscopists, and even in expert hands, it may sometimes be hampered by unsuspected and even insurmountable problems. Failed cannulation is reported in up to 20% of cases^[1], and increases the risk of most complications relevant to ERCP^[2]. Although “no size fits all”, some of the techniques of selective biliary cannulation are universally useful and their special features and challenges, as well as the evidence to support them, are described in the following.

STANDARD CANNULATION

Papillary access and positioning

The passage of the duodenoscope into the second part of the duodenum and positioning it appropriately is usually not a challenge beyond the first training cases, but on occasion it can pose its own difficulties. Anatomical variants, such as cascade stomach or huge hiatal hernia, may complicate traversing the stomach, left-sided liver resections may hamper the passage of the pylorus and duodenal bulb, and gastric outlet obstruction or duodenal stenoses may also pose problems. Positional change, evacuation of air from the stomach, and on occasion guiding catheters or even large caliber balloon placement deep in the duodenum can facilitate the passage of the endoscope.

Papillary assessment

Visualizing the papilla is also mostly straightforward. However, duodenal obstruction, mucosal edema (e.g., in the setting of acute pancreatitis), aberrant position of the papilla or periampullary diverticulum may be a challenge. In most cases, minute observation of the duodenal wall, together with identification of the longitudinal mucosal fold leading up to the papilla, will succeed, even for papillae hidden under a fold or inside a diverticulum.

Once in position, care must be taken to observe the anatomy of the papilla, particularly as regards size, papillary orifice, and assumed direction of the bile duct. Once manipulated with the catheter, these may all change, and the native appearance is the most useful one. Photo-documentation is helpful for potential repeat procedures.

Guidewire cannulation

Cannulation can be done with a variety of catheters, and include a variety of guidewires^[1]. Increasingly, however, a standard sphincterotome is used, for two reasons: the added utility of bending (+/- rotation) allows for a wider variety of targeting angles, and in the majority of ERCP procedures, a sphincterotomy will be performed as part of the therapeutic measures anyway. Thus, other special variants (e.g., super-tapered catheters, double-bending catheters, etc.) have a limited role today.

The bent sphincterotome tip can usually be rotated to the desired angle, which for the bile duct is normal around 11 o'clock [Figure 1]. However, care must be taken to relate this to the direction of the upward ductal impression if visible, or the orientation of the duodenal lumen.

For many years, wire-guided *vs.* contrast-guided cannulation have been compared and debated. Initially, contrast guidance was the only option, but with the increasing role of guidewires, their use also for cannulation has gained momentum. The concern with contrast has been the potentially harmful effect of inadvertent pancreatic contrast injection. Additionally, the guiding/stiffening role of the guidewire prior to catheter insertion may simplify the entry and increase the chance for successful access.

A number of comparative studies have been published, with all the inherent pitfalls in non-blindable technique comparisons^[3]. Most reviews and meta-analyses conclude that guidewire-assisted cannulation is

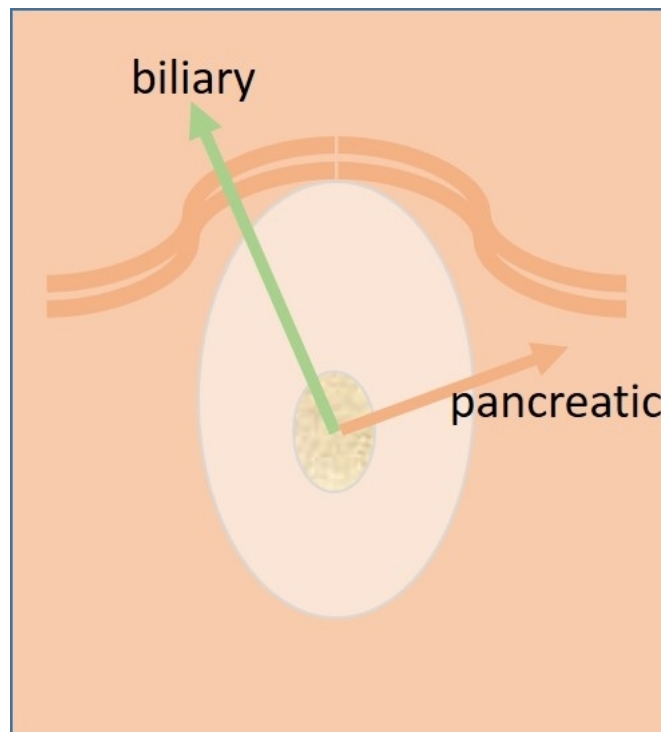


Figure 1. Principal directions of the biliary and pancreatic ducts from the papillary orifice.

associated with a higher cannulation success rate, as well as a lower overall risk of post-ERCP pancreatitis (PEP)^[4]. Consequently, the current European guidelines support this as the method of choice^[2]. However, in difficult cases, delicate injection of a small amount of contrast may outline the detail of mural intraduodenal ductal anatomy, without significant pancreatic contrast filling. This can then guide the subsequent guidewire manipulation in the appropriate direction.

Two variants of the wire-assisted technique, the “touch technique” and the “non-touch technique” are described^[4]. With the “touch technique”, the tip of the catheter is impacted gently into the papillary orifice in the appropriate direction, supporting the subsequent introduction of the guidewire. With the “non-touch technique”, the guidewire is positioned slightly protruding from the tip of the catheter and is inserted directly into the papilla and subsequently bile duct. This offers less support, but potentially avoids the mechanical distortion of the papillary anatomy that catheter impaction may cause^[5]. One randomized controlled trial (RCT) comparing the two indicated a better cannulation success with the touch-technique, albeit with a higher risk of inadvertent pancreatic cannulations^[6]. Most likely, both may have advantages depending on the papillary anatomy and experience of the endoscopist.

Once the guidewire passes, the direction will indicate what duct has been accessed, with the 11-12 o'clock direction towards the liver indicating biliary access. Care must be taken however, especially in the context of ampullary or pancreatic head tumors, where ductal anatomy may be distorted, or false routes can occur in the setting of necrotic tumors. Careful contrast injection will help confirm the situation.

As for the choice of guidewire for cannulation purposes, a number of options exist, in terms of caliber, material and shape^[4]. For main papilla cannulation, the shape and tip stiffness are probably the primary concerns. It has been suggested that smaller is of benefit, but comparisons have failed to corroborate this^[7],

and the lesser axial support of thinner wires may be a disadvantage in subsequent maneuvers. Again, choice mostly comes down to personal preference and experience. A special variant for cannulation support, the “loop-tip” guidewire, was introduced to support passage through the crevices of the papilla^[8], but it has since been discontinued.

DIFFICULT CANNULATION

The majority of cannulation attempts are straightforward in expert hands, even in native papillae. However, difficulties occur for both expected and unforeseen reasons. Difficult cannulations add to the risk of complications^[9], and much effort has been channelled into this area since predicting difficult cannulations might allow pre-emptive measures to minimise adverse outcomes.

A variety of definitions have been suggested for what should be considered difficult. Since it is not always based on identifiable pre-procedural factors, recent definitions are instead based on features of the actual cannulation attempt. A study from Scandinavia looked at 907 ERCPs in native papillae in a multicenter study^[10]. Allocating PEP as the determining factor, difficult cannulation was identified as > 5 min duration of attempt to cannulate, > 5 passes at the papilla, or > 2 guidewire passages into the pancreatic duct (PD). These three factors alone, or in combination, were associated with a significant increase in the incidence of PEP.

One important utility of such a definition is to aid the decision to change the initial strategy of standard guidewire cannulation. Further persistence with the same technique may finally succeed, but it is likely to increase the complication risk, so changing the strategy earlier should be considered.

There are number of alternative methods to achieve cannulation success that may be used instead of, or along with, the initial approach. Common to these techniques are that they require additional skills, add risk, but increase the chance of eventual cannulation success.

Double-wire technique

Not infrequently, attempts to access the bile duct result in inadvertent guidewire placement in the PD. If this recurs or results after substantial struggle, leaving it there and proceeding with cannulation alongside with another wire preloaded in the catheter, the “double wire technique” (DWT) is a viable option. In theory, the pancreatic wire stabilizes a mobile papilla, straightens the intraduodenal segment of the ducts, and potentially causes partial blockage of the PD, all components that may increase the chance of subsequent access to the bile duct. The method was introduced more than 20 years ago^[11] and has repeatedly been shown to improve cannulation success. The technique has been modified to include placement of a small-calibre transpapillary pancreatic stent over the guidewire already in the PD, resulting in significant protection from PEP^[12], and is currently recommended in recent ESGE guideline on ERCP adverse events^[13] whenever the DWT is used. Alternatively, a stent can be placed initially in the PD for subsequent alongside-cannulation or needle knife cutting on the stent.

DWT has been associated with increased risk of PEP. In a recent systematic review comprising 7 RCTs with difficult cannulation in 577 patients, the authors found a 2-fold increase in risk of PEP using the DWT, without increased cannulation success^[14]. However, like all problem-solving methods, it may falsely be blamed for the risk imposed by previous failed cannulation attempts. Also, most studies in that review were done prior to the standard use of rectal non-steroidal, anti-inflammatory drugs (NSAIDs) for PEP prophylaxis. The protective role of a pancreatic stent in combination with NSAIDs is not clear^[13].

Transpancreatic sphincterotomy

Another potential utility of a pancreatic access wire is to perform a wire-guided pancreatic sphincterotomy, effectively also cutting the common ampullary muscle. The technique allows for a more focused cut than the free-hand needle knife precut technique, probably reducing the risk of perforation, and frequently, the biliary orifice can be visualized on the left edge of the cut crevice. Alternatively, an additional transverse free-hand extension of the cut to the left can be performed. The method was spearheaded by the Helsinki group, who showed that the method compared favorably to free-hand precut in a large retrospective multi-center trial^[15]. More recently, a systematic review also concluded that the method offered a higher cannulation success rate compared to the relevant alternatives, with a similar complication rate^[16]. A recent randomized comparison found a comparable PEP risk, but a higher cannulation success rate (85% *vs.* 70%) in transpancreatic sphincterotomy *vs.* double-wire technique^[17]. Long-term follow-up data are lacking at this time.

Needle knife precut

Classic precut technique

Without PD wire access, utilizing a needle knife to gain access to the bile duct must be considered. In this technique, the roof of the papilla is dissected layer by layer from the top of the mound, in the assumed direction of the bile duct [Figure 1], until the whitish onion-skin appearance of the bile duct epithelium is evident. The orifice can then usually be identified as a tiny nipple downstream, for subsequent cutting or cannulation, usually with a guidewire^[18]. The method requires visual exposure of the tissues, so sufficiently deep dissection is necessary, while avoiding transmural cut with duodenal perforation. The feasibility and safety of the method depends on the size of the intraduodenal papillary portion, with small, flat or hidden papillae leaving less space for cutting^[2].

Data on precut success and safety vary widely, surely depending on technique and expertise, but also on timing, sooner being safer. Initial statements on increased PEP risk have been somewhat countered by more recent meta-analyses, particularly considering early precut *vs.* persistent cannulation attempts^[19]. Most studies and guidelines state the need for expertise to safely perform biliary precut, but the training phase obviously poses a concern. Precut does remain a potentially risky method and should not replace good cannulation technique.

Needle knife fistulotomy

Suprapapillary fistulotomy is incision of the bile duct above the papillary orifice, onto the duodenal protrusion of the bile duct, creating a direct fistular access to the bile duct independently of the papilla. Subsequent maneuvers can then be performed through this orifice, or prograde extension of the fistula across the papillary muscle can be made.

The method has the potential benefit of biliary access without touching the pancreatic orifice, thus reducing the risk of PEP. Indeed, in the meta-analysis by Choudhary *et al.*^[19], a distinct reduction in PEP was seen with this method. However, its feasibility depends on anatomical factors and ideally a dilated bile duct down toward the papilla, to increase the chance of successful bile duct puncture. Ampullary cancer represents a special situation where the method can indeed be useful^[20].

SPECIAL PROBLEMS

Periampullary diverticula

Duodenal diverticula are relatively common, particularly in elderly patients^[21]. Moreover, both advancing age and the presence of the diverticulum promote the preferential growth of glucuronidase-producing bacteria predisposing to the formation of gallstones^[22]. Periampullary diverticula with an extradiverticular

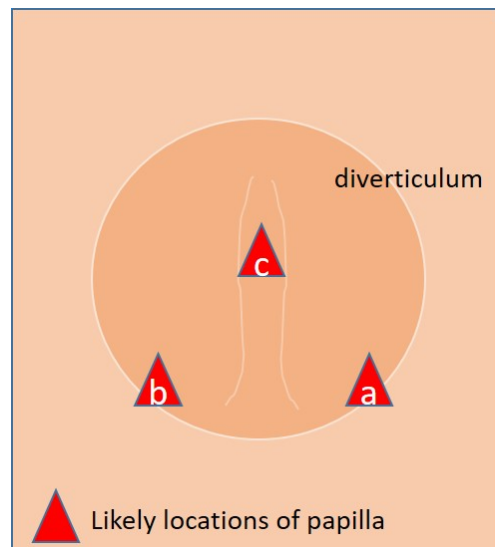


Figure 2. Likely locations of intradiverticular papillae, at (a) 5 o'clock, (b) 7 o'clock or (c) on an intradiverticular ridge.

position of the papilla rarely cause concern, although the trajectory of the ducts may change. Intradiverticular papillae can be more difficult to locate and approach, particularly those located on the inner edge of the lower rim. Mostly, intradiverticular papillae can be found at the lower edge, 5 o'clock or 7 o'clock, or on central intradiverticular fold, if there is one [Figure 2]. Entry of the diverticulum with the tip of the scope is helpful if feasible, otherwise, clipping, mini-biopsy forceps alongside the cannulating catheter or saline injection to lift the papilla forward may all help in facilitating the cannulation. Inadvertent wire passage into the pancreatic duct should always be retained for added support and subsequent biliary access. In general, published results indicate a similar success rate in these patients^[23], although time spent may be longer.

Billroth II anatomy

Billroth II resections were prevalent as definitive peptic ulcer therapy in the pre-PPI era, but we still see these patients occasionally presenting for ERCP. Access is usually feasible with a standard duodenoscope, although fixations in the afferent loop may pose a risk for perforation during intubation and justify the change to an enteroscope. A standard gastroscope or pediatric colonoscope with a cap are valid options, but manipulation at the level of the papilla are more cumbersome. With a side-viewing instrument, positioning at the papilla is usually straightforward, although the access from below renders everything upside down. This also makes the standard sphincterotome less useful because the direction of the bending and the cutting wire end up on the wrong side. Usually, a straight standard catheter with a guidewire is preferable for cannulation. For sphincterotomy, special inverted sphincterotomes are available, but needle knife cutting over a temporary short plastic stent may be a more available and simpler alternative^[24].

Other anatomy - intact papilla

Gastric resection (for cancer) and diversion (bariatric gastric bypass) both comprise a Roux-en-Y loop connected to the distal esophagus, with a reconnected jejunal loop of variable length leading to the duodenum from below, similar to the Billroth II anatomy. This situation presents access challenges, as well as issues at the level of the papilla.

In these cases, device-assisted enteroscopes are usually necessary^[25]. Access to the entero-enteric anastomosis is usually straightforward, avoiding the passage of the stomach and ligament of Treitz. With visual control of the anastomosis, the correct loop would be the one connected to the blind loop, usually at an acute angle to the scope direction. Further passage will be variably complex depending on the length of the loop and the Treitz angulation, or other fixations may be additional challenges. Also, the amount of small bowel loops makes tip manipulation limited. Typically, the access to the papilla requires a 180 degrees angulation at the level of the lower duodenal knee. A cap on the scope tip facilitates manipulation of the papilla and is mostly helpful. Regardless, cannulation (usually with a straight catheter) is a challenge, also given the lack of an instrument channel elevator on the enteroscope.

Published data confirm the technical challenges of access, as well as cannulation^[26]. Thus, percutaneous, hybrid laparoscopic approaches, as well as endoscopic ultrasound (EUS)-assisted approaches, are being explored, depending on the specific surgical situation^[27]. As these procedures become increasingly common and as weight loss predisposes to the formation of gallstones, data and technical developments in this important field are eagerly awaited.

Other anatomy - hepaticojejunostomy

The other relevant anatomical situation is a Roux-en-Y hepaticojejunostomy, either with an entero-enterostomy, e.g., after hepatobiliary surgery complications or liver transplantations, or after Whipple surgery. In both situations, enteroscopes are usually needed for enteric passage. However, biliary access via a hepaticojejunostomy is usually less demanding, although identification, as well as cannulation of strictured anastomoses may be a challenge. Again, EUS-guided alternatives are being explored, particularly for palliative situations.

Other options

After prolonged failed attempts at biliary cannulation, the endoscopists must always consider alternatives: call a friend or stop and try another day. Depending on the urgency of the clinical situation, the reasons for failure and the access to more experienced colleagues are both options that must be considered. The overall benefit of the patient must be paramount. If drainage is urgently needed, EUS-guided, as well as percutaneous techniques must also be considered, depending on available expertise.

Conclusions

Most biliary cannulations are straightforward given the appropriate expertise. However, difficulties occur because of specific anatomical difficulties or even because of specifics of the papillary anatomy. Comprehensive understanding of the situation, and appropriate command of the various problem-solving options are mandatory and must be part of the procedural armamentarium of all endoscopists performing ERCP.

DECLARATIONS

Authors' contributions

Developed the concept, researched the field, and prepared the manuscript: Aabakken L

Developed the concept, researched the field, and edited and supplemented the manuscript: Bhat P

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Conflicts of interest

Both authors have 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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Comparison of open and laparoscopic inguinal hernia repair

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Abstract

Inguinal hernia repair is one of the most commonly performed general surgery operations. Throughout the years there have been many variations and advancements, including open and laparoscopic techniques, to accomplish the same task of reducing herniated contents and preventing groin hernia recurrence. An array of factors contributes to deciding which operative technique is the best approach to managing a patient presenting with an inguinal hernia. Published data vary due to the heterogeneity of techniques compared, patient presentations, and surgeon expertise. In experienced hands, laparoscopic repair results in a quicker return to work and reduced postoperative pain. Patients with bilateral groin hernias, female patients with groin hernias, and patients with recurrent hernias after prior anterior mesh repair should be offered a laparoscopic preperitoneal mesh approach, when surgeons have the appropriate skill set and experience. We find that open and laparoscopic techniques of inguinal hernias can both achieve exceptional outcomes when applied to the right patient population. To know one's own capabilities, it is beneficial for surgeons to have baseline familiarity of the multitude of methods of repair, become proficient in both mesh and mesh-free techniques as well as open and laparoscopic techniques to best tailor the surgery to the patient and the clinical circumstances, and follow personal outcomes to evaluate individual results.

Keywords: Hernia, inguinal, herniorrhaphy, laparoscopy, Lichtenstein

Inguinal hernia repair is one of the most common operations in general surgery, with over 700,000 inguinal



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hernias repaired in the United States annually^[1,2,3]. Throughout the years there have been many advancements in the operation including the genesis of laparoscopic techniques. With a multitude of surgical methods, it can often become difficult in deciding the best method of repair. An array of factors contributes to deciding which operative technique is best utilized for a patient presenting with an inguinal hernia. We will explore these variables as well as the surgical techniques themselves.

SURGICAL TECHNIQUES

Open inguinal hernia repairs can be categorized into two main categories: tissue repair and mesh repair [Table 1]. There are several named techniques that can be utilized for performing a tissue repair such as the Bassini, McVay, Marcy, and Shouldice repairs^[4,5,6]. The Desarda repair, a more recently described tissue repair, utilizes a partially detached strip of external oblique aponeurosis^[7]. For open mesh repairs, prosthetics are either placed anteriorly or preperitoneal. The gold standard mesh repair is the Lichtenstein tension-free mesh repair which places the mesh anteriorly between the external and internal oblique aponeuroses^[8]. Other open mesh techniques include the plug-and-patch, the Gilbert Prolene Hernia System (PHS) Bilayer connected device repair, and the open preperitoneal mesh placed via an inguinal incision after reduction of the hernia^[9,10]. The Stoppa repair, is an open preperitoneal mesh repair utilized for large inguinoscrotal and bilateral inguinal hernias, utilizing a lower midline incision^[11]. The anatomic exposure of the Stoppa repair is the precursor for laparoscopic preperitoneal repairs. These aforementioned open surgical techniques allow for repair both with and without mesh, as well as placing mesh in various locations.

By utilizing the preperitoneal space and exposure of the myopectineal orifice described by Rene Stoppa, laparoscopic approaches to inguinal hernia repairs are a minimally invasive option to inguinal hernia repair by placing mesh in the preperitoneal space. There are two main methods of laparoscopic inguinal hernia repair with the same exposure and coverage of the myopectineal orifice but differences in how access to the preperitoneal space is gained. One approach avoids violation of the abdominal cavity (Totally Extraperitoneal - TEP repair) and one enters the abdominal cavity (Transabdominal Preperitoneal - TAPP repair). For both the TEP and TAPP repairs, dissection should ensure the critical view of the myopectineal orifice which routinely exposes the inguinal anatomy allowing any direct, femoral, obturator, or indirect hernias to be identified and reduced^[12]. Although these laparoscopic methods necessitate mesh use, recent minimally invasive techniques utilizing robotic platforms may provide a means of mesh-free preperitoneal repair in selected patients with direct and/or indirect defects^[13].

In the TEP repair, surgery is contained within the extraperitoneal space. This can provide an advantage when patients have had prior abdominal surgeries with the potential of adhesions and scar tissue complicating the procedure, but still allowing for a minimally invasive approach. In the TAPP repair, surgery takes place from the intraabdominal space and subsequent access to the preperitoneal space is gained by incising the peritoneum and creating a peritoneal flap. The transabdominal view allows for a deliberate evaluation of intraabdominal contents, such as when there is concern for ischemic bowel. Unlike the TEP repair which is able to use insufflation between the abdominal wall and the peritoneum, the TAPP repair requires the surgeon to actively retract the peritoneum during dissection. When considering laparoscopic repair, surgeon experience and skill allow for replicability, decreased surgeon experienced difficulty, and reduction of complications - large trocar sites should be properly closed to reduce the risk of a subsequent trocar site hernia, the extraperitoneal space should carefully be created during a TEP repair to avoid tears and large holes which can complicate and hinder exposure, access to the abdominal cavity and pelvic exposure should be performed carefully to avoid enterotomies and/or injury to the peritoneum, and dissection of the hernia sac away from cord structures should be methodical to avoid damage to nearby

Table 1. Classification of open and laparoscopic techniques for inguinal hernia repair

		Open	Laparoscopic
Mesh-free tissue repair		Bassini Marcy McVay Shouldice Desarda	
Mesh repair	Anterior mesh	Lichtenstein Plug-and-patch Bilayer device (PHS)	
	Preperitoneal mesh	Open preperitoneal via inguinal incision Stoppa	TEP TAPP

TEP: Totally extraperitoneal; TAPP: transabdominal preperitoneal.

structures and creation of peritoneal holes.

LAPAROSCOPIC VS. OPEN

The argument of which method is superior - open or laparoscopic - is often had by surgeons. With the wide array of techniques, patient factors, and surgeon factors, determining applicability of published results to one's own practice can be quite difficult. Evaluating the type of open or laparoscopic procedures being assessed, the patients' surgical histories, hernia size and patient comorbidities, and investigating surgeons' expertise with each study all can be confounding variables that affect the results of a study and make meta-analyses quite difficult with such heterogeneous study methods. We would argue that it is beneficial for surgeons to have baseline familiarity of the multitude of surgical procedures, become proficient in both mesh and mesh-free techniques as well as open and laparoscopic techniques to best tailor the surgery to the patient and the clinical circumstances, and follow personal outcomes to evaluate individual results.

Surgeon familiarity with technique and anatomy is of utmost necessity to ensure good outcomes and avoid complications. Gaining expertise with the Shouldice technique's four layers is benefited by surgical repetition, as shown by the results from the study by Malik *et al.*^[14], which demonstrated repair at the high volume Shouldice Hospital was far superior to those from lower volume hospitals (1.15% vs. 5.21%). Although the 2012 Cochrane review found the Shouldice repair to be the best of all open mesh-free techniques, it took longer, required a longer hospital stay, and still had higher recurrence rates compared with mesh repair^[15]. Whereas only 36 Lichtenstein procedures were needed to gain proficiency with inguinal hernia repair^[16], it has been shown that as many as 250 laparoscopic hernia procedures are needed to attain sufficient experience to ensure similar complication rates relative to open repairs^[17,18]. Repetition of procedures increases competency, and exposure to nuanced differences, and, in turn, improves surgical skill and results.

Both the European Hernia Society (EHS) guidelines and the international guidelines for groin hernia management published by the HerniaSurge group in 2018, recommend open Lichtenstein and laparoscopic inguinal hernia repairs for nonrecurrent, unilateral inguinal hernias^[19,20]. Based on surgeon experience, open and laparoscopic repairs are acceptable methods. However, there are specific clinical scenarios in which certain procedures may be more advantageous than others such as contaminated or infected wounds, recurrent groin hernias, patients with contraindications to laparoscopy, and scenarios where multiple groin hernias are suspected.

CONTAMINATED OR INFECTED WOUND

For emergent or urgent cases in which there is gross contamination with pus or stool, a mesh free repair is necessary. Because laparoscopic inguinal hernia repair necessitates mesh use while open inguinal hernia repair can be performed both with and without mesh, an open tissue repair is the technique of choice for inguinal hernias in the setting of infection or stool spillage. Although biologic and absorbable synthetic meshes have been used in these settings, it should be cautioned that these meshes are not FDA approved for use in an infected field^[21]. For emergent or urgent cases with strangulated bowel requiring resection, where contamination is negligible, mesh use has been shown in small cohort studies to have acceptable surgical site infection rates^[22,23]. For contaminated settings, the senior author often prefers to utilize the Bassini or McVay tissue repair technique after wound irrigation and/or bowel resection. In cases of incarceration with possible strangulation, diagnostic laparoscopy with placement of ports for a TAPP repair is utilized to allow for intraabdominal evaluation of bowel. If viable, a TAPP repair is performed with a macroporous polypropylene mesh. If not viable, bowel resection is performed, and an open Lichtenstein repair is performed if contamination is well controlled; otherwise, a Bassini or McVay tissue repair is performed.

RECURRENT INGUINAL HERNIA

In recurrent hernia cases, the operating surgeon benefits from knowing the manner of the prior repair and utilizing the non-violated plane. Where the prior repair was performed using an open approach with anterior mesh, a laparoscopic technique is the recommended course^[20]. Where the prior repair was performed using a laparoscopic approach with preperitoneal mesh, an open approach with anterior mesh is recommended^[20]. In patients with multiply recurrent groin hernias where both anterior and preperitoneal planes have been violated, subsequent repair methods should be based on surgeon expertise. For these difficult scenarios, the senior author first reviews all old operative notes and obtains recent pelvic imaging with a CT scan for evaluation of anatomy. Based on this information, a repeat open repair may be tried on patients with a hostile abdomen or operative notes demonstrating a previous difficult MPO dissection. Otherwise, a repeat preperitoneal approach is tried, usually with the utilization of the robotic platform, which the author finds to be helpful in both visualization and ease of retraction of the peritoneal flap.

CONTRAINDICATIONS (AND RELATIVE CONTRAINDICATIONS) TO LAPAROSCOPY

The ability to perform an open repair under local or regional anesthesia negates any risk that could arise with general anesthesia. The insufflation of laparoscopy requires general endotracheal anesthesia (GETA) and thus any patient population in which GETA is contraindicated cannot undergo laparoscopic inguinal hernia repair. The higher risk of intra-abdominal adhesions and scarred tissue planes of patients with prior pelvic and/or abdominal surgeries can make laparoscopic approaches more difficult and potentially increase morbidity. For these reasons, open repair is often the repair method of choice as it rarely violates the abdominal cavity or requires extensive pelvic dissection. However, there are published studies in the appropriately skilled and experienced surgeon's hands, demonstrating that laparoscopic repair is safe and feasible in patients with prior pelvic and lower abdominal surgeries^[24,25].

MORE THAN JUST A UNILATERAL INGUINAL HERNIA

The Stoppa repair is the only open repair that allows bilateral groin hernia repair through the same incision as a unilateral repair and does not require bilateral groin incisions. For patients with symptomatic bilateral inguinal hernias, laparoscopic repair allows repair for both the right and left sides through the same three small trocar incisions. Indeed, in our practice, all patients without contraindications to laparoscopy and with bilateral groin hernias are offered a minimally invasive approach for repair. For patients with suspected contralateral hernias, a TAPP repair is offered to allow for contralateral inspection during initial camera insertion. TEP repair can also be performed, but contralateral exploration requires dissection of tissue

planes. In our practice, a thorough discussion is conducted with the patient preoperatively on the risks and benefits of concurrent repair of an asymptomatic contralateral hernia *vs.* waiting until symptoms develop to pursue repair. Based on patient preference, repair of the contralateral asymptomatic side may or may not be performed.

In reviews of both the Swedish and Danish hernia databases, femoral hernias were found in over 40% of surgeries for recurrent groin hernias in women^[26,27]. The preperitoneal dissection and the evaluation of the myopectineal orifice in laparoscopic repair ensure any occult femoral hernias are evaluated and treated with the mesh covering the space. For this reason, the EHS and Herniasurge groups encourage laparoscopic groin hernia repairs in female patients, to reduce the risk of missed femoral hernias in open repairs where the floor is commonly not opened and explored^[19,20]. In our practice, female patients with groin hernias are preferentially offered a laparoscopic or minimally invasive technique. If an open repair is performed, the femoral space is always explored, evaluated, and repaired if necessary, using a modified Lichtenstein technique.

COSTS OF REPAIR

Costs for inguinal hernia repair have been shown to be significantly lower for open inguinal hernia repair, with differences being attributable to operating time as well as disposable material costs. As with many cost calculations, results should be well scrutinized to determine applicability to a surgeon's and patient's specific circumstances, the items being included in cost estimates, and the time frame for which costs are evaluated. In the 2006 VA study evaluating overall healthcare costs over 2 years (including operative costs, subsequent inpatient and outpatient care, and medications), Hynes *et al.*^[28] found laparoscopic repair was on average \$638 more than open, though not statistically significant. Similarly, in the retrospective study by Spencer Netto *et al.*^[29], open unilateral inguinal hernia repair was found to be significantly cheaper than laparoscopic repair (median total cost, \$3207.15 *vs.* \$3723.66; $P < 0.001$), while bilateral repair costs were almost similar (median total cost, \$4574.02 *vs.* \$4662.89; $P = 0.827$). In a prospective randomized control trial (RCT) by Feliu *et al.*^[30], laparoscopic bilateral inguinal hernia repair was found to be faster, with shorter hospital stays, fewer recurrences, and lower postoperative complications than bilateral inguinal hernias repaired using the Lichtenstein technique. In a meta-analysis by Schmedt *et al.*^[31], operative time for a unilateral open Lichtenstein repair was significantly shorter than laparoscopic repair (55.5 min *vs.* 65.7 min; $P = 0.01$)^[27]. Due to variation in negotiated reimbursement rates, institutional cost evaluations by Jacobs and Morrison showed \$731 higher income generation for an ambulatory surgery center with laparoscopic repair when compared to open, despite increased disposable costs of laparoscopic repair materials^[32]. Although repair of unilateral groin hernia repair may be cheaper when performed open, it may net the performing institution more income when performed laparoscopically. It does appear that bilateral repairs performed laparoscopically are financially better. With the reduction of operative times and decreased costs of disposable materials, use of laparoscopy could become similar if not more financially reasonable for the repair of unilateral inguinal hernia repairs as well. By knowing personal operative times and hospital costs, surgeons can adjust their surgical techniques to make the most financially reasonable as well as clinically appropriate decision.

COMPLICATIONS

As previously stated, familiarity and expertise with a surgical technique are also reflected in surgical outcomes. Well conducted studies and published analyses provide varying results on laparoscopic and open inguinal hernia repair. In the 2004 RCT by Neumayer *et al.*^[17] with the Veterans Affairs (VA) medical centers, comparing open mesh repair to laparoscopic mesh repair, the laparoscopic repair group had lower postoperative pain and quicker return to normal activities, but higher rates of complications and

recurrences. These findings have been questioned, as the size of the mesh used for laparoscopic repair was not standardized and may have played a role in higher laparoscopic recurrences^[33]. As well, the study included operating surgeons not sufficiently adept at laparoscopic repair (only 25 prior repairs were needed to qualify as a surgeon in the study) and posthoc analysis found significant differences in recurrence rates between surgeons who had performed fewer than 250 laparoscopic repairs *vs.* those who had performed greater than 250 repairs (> 10% recurrence *vs.* < 5% recurrence; $P < 0.001$)^[17]. In the 2010 meta-analysis by Karthikesalingam *et al.*^[34] of four RCTs comparing various open repairs to laparoscopic (TEP and TAPP) inguinal hernia repair, recurrence rates, chronic pain, hematoma formation, and need for additional operations were the same, while laparoscopic repair had less postoperative pain, fewer wound infections, faster recovery and return to work, but a longer operative time. In the 2005 meta-analysis by Schmedt *et al.*^[31] comparing laparoscopic (TEP and TAPP) techniques to the Lichtenstein repair, laparoscopy had lower rates of wound infection, hematoma formation, nerve injury and chronic pain, and quicker return to work and daily activities, while open repair had fewer recurrences and seromas, and shorter operative times. In further analysis with removing the results from the 2004 Neumayer study, regarding the difference in recurrence rates of open and laparoscopic repairs, there was no statistically significant difference between laparoscopic and open repairs^[17,29]. Consistently seen in these studies, laparoscopic repair appears to have quicker return to work as well as less postoperative pain.

WHEN TO UTILIZE EACH TECHNIQUE

There are many variables to take into consideration, such as patient gender, type of groin hernia, wound class, whether it is unilateral or bilateral, and prior surgeries, when deciding on the method of repair. As well, a surgeon must take into account personal expertise with each surgical technique and determine the best type of repair for the clinical scenario. With that acknowledgement, in order to develop expertise, surgeons must progress through a learning curve and necessitate the need to accept longer operative times, higher costs when using adjunct disposables such as a dissecting balloon for TEP repair, and potentially higher incidences of complications such as seromas and hematomas. Once a surgeon feels competent with both laparoscopic and open techniques, an evaluation of personal outcomes should be made to determine what is the best method of repair to offer each patient. With equal expertise in open and laparoscopic repairs and evaluation of published data, patients with bilateral groin hernias, patients suspected of contralateral groin hernias, female patients with groin hernias, and patients with recurrent hernias after prior anterior mesh repair are offered minimally invasive and/or laparoscopic repair [Figure 1]. Patients with contraindications to general anesthesia or prior preperitoneal repair are offered an open Lichtenstein repair. Men with unilateral non-recurrent groin hernias or patients with histories of pelvic surgery and scarring are offered both open and minimally invasive/laparoscopic repairs, and differing risks and benefits are evaluated and weighed by the patient and surgeon to determine a mutually agreed upon method of repair.

There are many possible interventions when addressing inguinal hernias. There are variations of both open and laparoscopic techniques - from mesh to tissue repair and transabdominal to totally extra-peritoneal. Each surgeon must consider patient factors along with their own skill set and comfort level when deciding which technique to use. It is beneficial for surgeons to be well acquainted and facile with both open and laparoscopic techniques to provide a tailored approach to each patient. Like most things, the fact that there are multiple ways to perform a procedure is indicative that there may not be one truly best way. Equally important is that the surgeon becomes facile with the surgical technique, is knowledgeable of the anatomy and surgical principles of the operation, acknowledges the clinical situation, and follows the patients' outcomes.

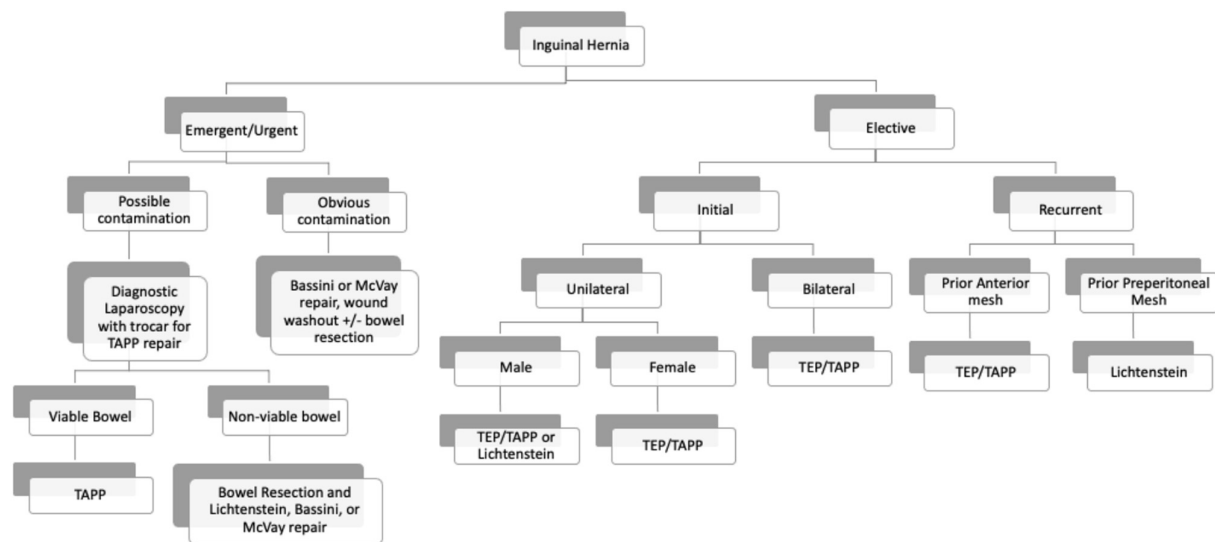


Figure 1. Algorithm for inguinal hernia repair based on current literature. TEP: Totally extraperitoneal; TAPP: transabdominal preperitoneal.

DECLARATIONS

Authors' contributions

Made substantial contributions to literature review, manuscript writing, and editing: Burton V, Perez AJ

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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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Consent for publication

Not applicable.

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Technical Note

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Management of hernial orifices in robotic inguinal hernia repair

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Abstract

The development of a postoperative seroma after endoscopic transabdominal (TAPP) or extraperitoneal (TEP) groin repair is a frequent problem. Although seromas are usually only mildly symptomatic, the swelling that develops postoperatively often causes patients to feel insecure and worried. In the literature some technical approaches to reduce the incidence of postoperative seroma are described. This technical note deals with the authors' approach in the management of large medial and lateral hernial orifices during robotic r-TAPP procedures using DaVinci Xi technology with the aim of seroma prophylaxis.

Keywords: Inguinal hernia, robotic surgery, hernial orifices, seroma, barbed suture, TISSEEL, fibrin sealant

INTRODUCTION

The postoperative occurrence of seroma is a challenge after inguinal hernia repair and often leads to insecurity and concern of patients, who may misinterpret the postoperative swelling as an early hernia recurrence, a finding also known as pseudo-recurrence. In some cases, the seroma can also affect the nerves of the groin region and lead to increased postoperative pain or even the development of a chronic pain syndrome^[1]. Despite the usual spontaneous remission of seromas in the course of a few weeks, it is reasonable to find strategies to reduce the risk of postoperative seroma formation. The reported incidence of postoperative seroma varies between 0.5%-12.2%^[2].



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Both, the morphology of the hernia and the surgical technique have been shown to influence postoperative seroma formation. In a large register-based study with more than 20,000 groin hernia patients treated by transabdominal pre-peritoneal (TAPP) laparoscopic techniques, multivariate analysis indicated that medial hernias and large hernias (EHS type 2 and 3) were associated with a significantly higher occurrence rate of seroma. Further, the method of mesh fixation was shown to have an impact; meshes fixed with fibrin glue had higher seroma rates than meshes fixed with staples. The risk of seroma was lowest if the mesh was not fixed at all^[3]. There are some specific surgical measures intended to prevent seroma formation; an overview of the outcome of some of these techniques is presented in the systematic review by Li *et al.*^[4].

Generally, 2 areas of interest for prophylactic measures regarding seroma formation have been investigated. First, the medial hernial orifice with the weakened transverse fascia in large hernias can be targeted. A low rate of postoperative seroma has been achieved both by tightening the transverse fascia with an endoloop^[5] as well as with a V-Loc suture^[6]. Secondly, in the area of the lateral hernial orifices, the application of fibrin glue spray into the inguinal canal has been investigated, showing a reduction in size and rate of postoperative seromas^[7]. Although the placement of surgical drains may reduce the risk of postoperative seroma formation, its routine use is not recommended by the European Hernia Society^[2].

The quality of all available studies on the management of hernia orifices during endoscopic inguinal hernia repair is limited due to the small number of patients examined. It can therefore be assumed that the techniques presented here have not yet been widely adopted. The recent introduction of robotics into endoscopic inguinal hernia repair promises large advantages, mainly the easiness to suture, the unprecedented accuracy and precision of the instruments use and the advantages of immersion view. First results pointing in this direction have recently been presented in a study where a suture retraction of the transverse fascia was performed in a total of 67 robotic TAPP (rTAPP) procedures, with no seroma nor other complication being recorded in the 30-day follow-up^[8].

The use of DaVinci technology makes it possible to perform not only precise, nerve-sparing tissue dissection and mesh placement, but allows also easy and efficient treatment of the hernial orifices for seroma prophylaxis as part of robotic inguinal hernia treatment. In the following, the authors' standardised approach for the treatment of hernial orifices in robotic inguinal hernia treatment is described in more detail.

Tailored approach

In the authors' hospital, robotic inguinal hernia repair by rTAPP is the standard procedure; since May 2018, we have performed more than 600 rTAPP procedures. Complementary to the usual surgical steps, we make an additional effort to optimize the treatment of the hernial orifices in selected cases. In doing so, the hernias are classified intraoperatively in line with the EHS classification, according to the anatomic location (L = lateral; M = medial; F = femoral) of the hernia and the size of the hernial orifices (1 = \leq 1 finger; 2 = 1-2 fingers; 3 = \geq 3 fingers)^[9]. We focus on large medial orifices (EHS type M2 and M3) and lateral hernias with large hernia sac or large lipoma (EHS type L2 and 3) as well as inguinoscrotal hernias. Although waiving of mesh fixation has been shown to result in lower rates of postoperative seroma in the literature^[3], it is also associated with an increased risk of recurrence, especially in large hernias. Therefore, in the author's series, mesh fixation is performed in all patients, although neither with glue nor with tacks, but with sutures. The robotic technology enables to perform mesh fixation with precise, superficially stitched, and loosely knotted absorbable sutures, without the risk of nerve damage.

Surgical treatment of the medial hernial orifice

The medial hernial orifice is treated in large direct hernias (EHS M2 and M3) and/or if a considerable weakness of the transverse fascia exists. The fascia transversalis is progressively plicated or sutured to the iliopubic tract with a V-Loc suture; the suture is progressively performed concomitantly to the removal of the fatty tissue before the fascia is blown outwards by the pressure of the pneumoperitoneum. This approach takes some time (~5-8 min) due to the repetitive change of instruments (scissors/needle driver), but allows a very precise handling of the tissue, eliminating the risk of injury to the spermatic vessels, the cord, or nerve structures of the inguinal canal [Figures 1-3].

Surgical treatment of the lateral hernial orifice

In case of voluminous lateral hernias (EHS L2 and L3 with large hernia sac or lipoma) and in cases of scrotal hernias, the inguinal canal is sealed via the inner inguinal ring using fibrin glue spray (Tiseel, usually 4 mL). For this purpose, a specific flexible cannula is available [Figures 4-6]. This step increases the operative time by approximately 3-5 min. The application of the fibrin glue has to be performed by a scrubbed-in assistant familiar with the procedure.

Mesh fixation

In the authors' institution, mesh fixation during robotic rTAPP is performed in all cases. The robotic technology allows a minimally traumatic fixation of the mesh with four loosely knotted stitches with resorbable suture material (Vicryl 3-0). The location of the four sutures is as follows: (1) Cooper's ligament; (2) fascia of the rectal muscle; (3) fascia of the transverse muscle; and (4) iliac fascia [Figures 7-9]. Even the suture of the mesh to the iliac fascia in the location of the triangle of pain, can be very safely applied due to the excellent visual control helping to protect and exclude the nerves that are localized just below this fascia (i.e., N. cutaneous femoris lateralis and femoral and genital branches of the genitofemoral nerve) [Figure 8].

CONCLUSION

The treatment of the medial and lateral hernia orifice as part of endoscopic inguinal hernia treatment for postoperative seroma prophylaxis seems to be reasonable, especially in the case of large hernias. The use of DaVinci technology makes it thereby easier to apply the here presented techniques with utmost precision and accuracy.

The described 4-point suture fixation technique for the rTAPP with absorbable sutures is safe, according to the authors' experience. Skipping fixation with the inherent risk of mesh migration and hernia recurrence should not be advocated any more in times of robotic technology. A randomized evaluation of the described techniques in terms of postoperative seroma formation, chronic pain, or recurrence has yet to be performed. However, our preliminary, unpublished data concerning the strategies described above shows no elevated rates of chronic pain, no recurrence, and a clear decrease of the incidence of seroma.

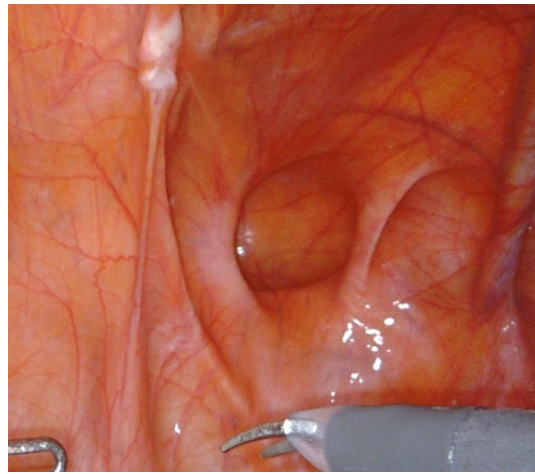


Figure 1. Initial situation with a right sided large direct hernia (EHS M3).

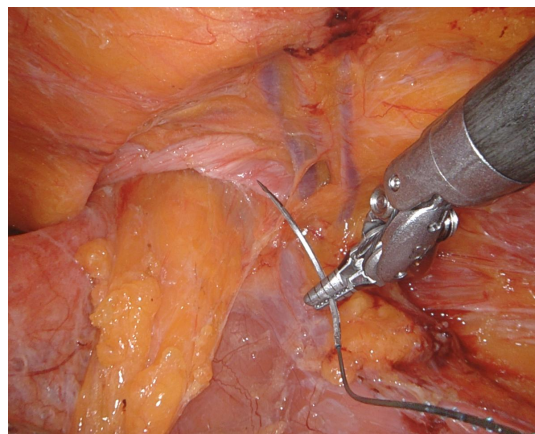


Figure 2. The suture of transverse fascia is performed step-by-step in alternation with the gradual mobilisation of the fatty tissue. In doing so, the surgeon can be sure that the suture does not damage vessels, nerves or the deferent duct, structures that are very close to the fascia transversalis. This prevents excessive protrusion of the transverse fascia into the groin during dissection (right side repair).

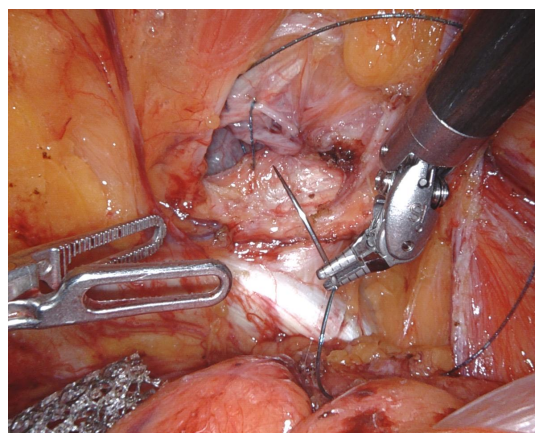


Figure 3. Suturing of the transverse fascia down to the iliopubic tract with a running V-Loc suture (right side repair).

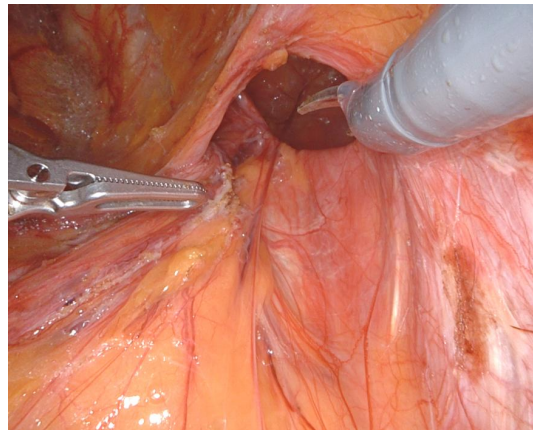


Figure 4. Lateral, right sided hernia with a large hollow space in the deep, due to the reduction of a respective lipoma and the outer sac. Prior to removal of the right instrument (scissors), it is positioned at the level of the inner ring, to facilitate later guidance of the fibrin glue application cannula by a correct angel of the trocar; this way, the 8 mm DaVinci port remains connected to the respective DaVinci arm.

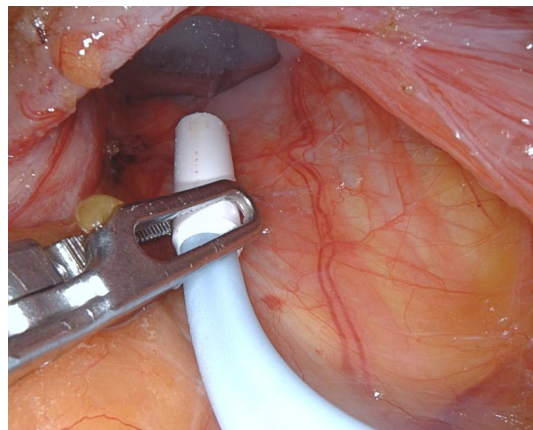


Figure 5. Endoscopic view into the inguinal canal with the Tisseel applicator already in place. The fibrin application cannula is guided by the Prograsp forceps. With the wrist movements of the Prograsp, the fibrin glue can be sprayed in all directions, covering the whole inner surface of the tissues of the inguinal canal (right side repair).

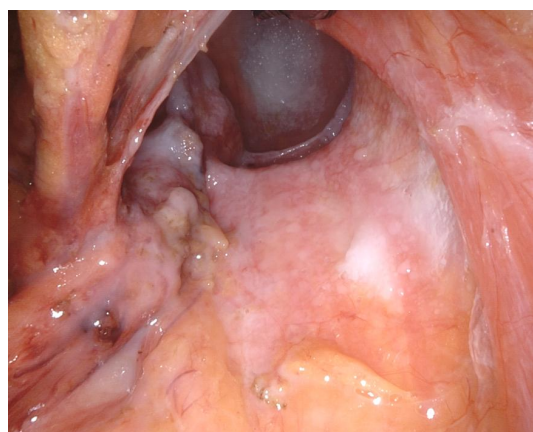


Figure 6. Inguinal canal lined and sealed with fibrin glue spray. With the 30° optic the result can be visualised deep into the hollow space (right side repair).

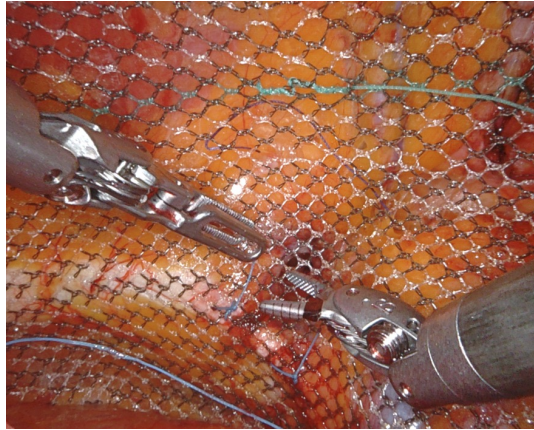


Figure 7. Mediocaudal fixation of the mesh to Cooper's ligament (ligamentum pectinatum) (right side repair).

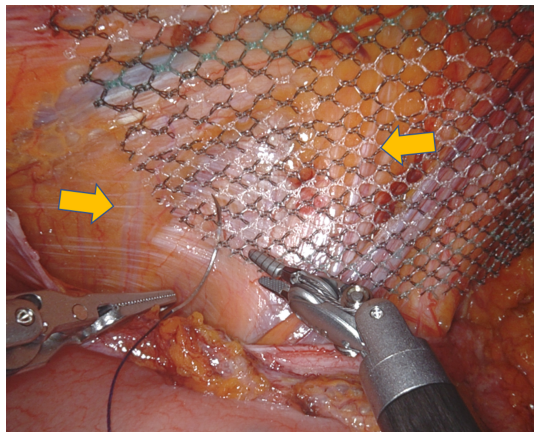


Figure 8. Laterodorsal fixation (left side repair). The fixation is done by a very superficially stitched suture including only the iliac fascia, with safe exclusion of the clearly visible nerves (yellow arrows) of the lateral abdominal wall.



Figure 9. Mesh fixed with 4 single sutures (right side repair).

DECLARATIONS

Authors' contributions

Collecting imaging material and manuscript writing: Baur J, Ramser M, Dietz UA

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Dietz UA is proctor for Intuitive. All other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The scientific analysis of patient data in the authors' clinic is covered by an ethical vote of the University of Basel (EKZN 2019-02046). Patients have consented to the use and publication of their medical data collected in the course of medical care for scientific purposes.

Consent for publication

Patients have consented to the use and publication of their medical data collected in the course of medical care for scientific purposes.

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Review

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Urinary diversions for radical cystectomy: a review of complications and their management

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Abstract

Radical cystectomy involves a urinary diversion, the most used being the ileal conduit and the orthotopic neobladder. This review focuses on the complications associated with these procedures, dividing them into general and diversion related complications, as well as their management. We conducted a search on PubMed and Scopus to identify eligible articles on complications of urinary diversions. Randomized controlled trials and systematic reviews with meta-analysis were preferred when available. Early complications occur in the first 90 days after surgery. The most common is post-operative ileus, followed by urinary tract infections and urinary leakage. Most complications occur in the late post-operative setting, being related to the type of urinary diversion. Some of these complications are renal failure, metabolic abnormalities, infections, urolithiasis, and ureteroenteric strictures, each with particular management options. Specific ileal conduit complications are conduit deformities and parastomal hernias. Neobladder patients can have continence problems, like incontinence or urinary retention, but also fistulas and dehiscence. Standardization of complications' definitions and time-dependent reporting are crucial to better understand and manage these complications. Complication rates are similar between open and robot-assisted procedures and between intracorporeal and extracorporeal diversion. Radical cystectomy with urinary diversion is the most difficult surgical procedure in urology with high early and late complication rates. There is an urgent need of standardizing complication reporting to better compare different procedures.



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Keywords: Urinary diversion, ileal conduit, orthotopic neobladder, cystectomy, urinary bladder neoplasms, complication

INTRODUCTION

Radical cystectomy for the treatment of bladder cancer implies a urinary diversion for replacement of the lower urinary tract, which nowadays can be created in an extracorporeal or minimally invasive totally intracorporeal way. The ideal urinary reservoir would be a low-pressure system, storing approximately 500 mL of urine, with complete continence, complete voluntary control of voiding, and minimal absorption of urinary waste products^[1]. The variety of urinary diversion types underlines the absence of an ideal one. They can be divided into noncontinent and continent diversions. Noncontinent cutaneous diversions include cutaneous ureterostomies and bowel conduits; continent diversions can be cutaneous, with a catheterizable pouch, or orthotopic, as the famous neobladder. The most used urinary diversions are the ileal conduit and the orthotopic neobladder, which will be the focus of this review. Both have specific complications which will be discussed, as well as their management. They can be created by an extracorporeal open approach or in a minimally invasive totally intracorporeal way, with similar complications. The complication rates described in this review are summarized in [Table 1](#). Comparing diversions is beyond the scope of this review.

METHODS

A search using the keywords “radical cystectomy”, “urinary diversion”, “neobladder”, “ileal conduit”, and “complications” was conducted on PubMed and Scopus to identify eligible articles. We focused primarily on randomized clinical trials and systematic reviews/meta-analysis when available, but we mostly included retrospective studies, case series, and case reports. We also used the “snowball method”, involving tracking references of the previously chosen articles to identify additional relevant studies. Only articles in English, Portuguese, and Spanish were reviewed.

GENERAL COMPLICATIONS

Early post-operative complications (90 days)

Surgical morbidity is always dependent on correct reporting of the complications, and radical cystectomy with urinary diversion rates is an area where this is particularly evident. Studies show a wide range of early post-operative complication during the first 90 days (20%-80.5%), of both open or robot-assisted radical cystectomy (RARC)^[2-5]. The lack of standardized complication definitions may be one explanation for this discrepancy.

Gastrointestinal complications like ileus or small bowel obstruction and infectious complications are the most frequent^[2-4,6]. The “robot-assisted radical cystectomy vs. open radical cystectomy in patients with bladder cancer” (RAZOR) clinical trial showed no differences between early complication rates for open (67%) vs. robot-assisted procedures (69%), even when only major complications were considered. All the urinary diversions in the RAZOR trial were performed extracorporeally, which can influence complication results^[6]. However, performing the urinary diversion in an extracorporeal or intracorporeal way also carries similar complication rates, with a trend towards less gastrointestinal complications in the intracorporeal urinary diversion^[7,8]. Early complications are less related to the type of urinary diversion than late complications^[3].

Ileus

Post-operative ileus can have a multitude of definitions, but the most used is “the inability to tolerate solid

Table 1. Overall complication rates reported by the cited articles

General complications		Specific complications	
Early (90 days)		Ileal conduit	
Ileus	12%-23%	Parastomal hernia	11%-17.1%
Urinary tract infection	5.7%-44%	Conduit deformities	
Urinary leakage		Strictures	2.4%
Uretero-ileal	2%-5.5%	Neobladder	
Urethral	< 25.3%	Rupture	< 1%
Late		Fistula	
Renal failure	19%	Neobladder-enteric	< 2%
Metabolic abnormalities	< 50%	Neobladder-vaginal	2.7%-8.8%
Acidosis	10.2%-33%	Hypercontinence	
B12 deficiency	3%	Male	4%-8%
Urolithiasis	3.5%-15.3%	Female	24%-62.5%
Ureteroenteric stricture	1.3%-10%	Incontinence	
		Daytime	3%-43%
		Nighttime	< 54.7%

food by post-operative day 5, the need to place a nasogastric tube (NGT), or the need to stop oral intake due to abdominal distension, nausea, or emesis". In a study by Shabsigh *et al.*^[3], 23% of patients suffered from ileus by this definition. Hautmann *et al.*^[4] also used this definition to report an ileus rate of 12% in a large neobladder series of 1013 patients. In the RAZOR trial, the rate of ileus in open and robotic cystectomy was similar, 20% and 22%, respectively^[6]. A comparison between extracorporeal and intracorporeal approaches showed less time to return of bowel activity in intracorporeal robot-assisted diversions, which the authors attribute to less pain and analgesic use and faster return to normal activity due to smaller and less painful incisions and to less ambient air exposure of the peritoneum and abdominal viscera^[8].

Enhanced recovery after surgery (ERAS) protocols for cystectomy play an important role in reducing post-operative ileus, with a multimodal approach to prevent this complication which frequently prolongs hospitalization. Chewing gum and post-operative nasogastric tube avoidance, for example, seem to be effective in reducing ileus^[9,10].

Urinary tract infection

Urinary tract infections (UTIs) are a common complication causing readmission in many cystectomized patients. Early post-operative UTI rates range from 5.7% to 44%, but a lack of standardization is evident, and the rates greatly depend on the UTI definition. Diagnosing a UTI in a patient with a urinary diversion requires a high level of suspicion because of its vague presentation, ranging from abdominal discomfort and changes in urine's smell to septic shock. Most often UTIs occur before stent removal, and their higher frequency in the early vs. late post-operative period also suggests an important role of these foreign bodies in UTI pathogenesis. Antibiotic treatment should be directed to cultured microorganisms as soon as possible^[11-13].

Clifford *et al.*^[11] reported a global rate of 11% patients develop UTIs in the first 90 days post-operatively, predominantly by Gram-negative rods; 17% of those patients had recurrent infections and 20% had urosepsis. They studied UTI rate by type of urinary diversion and found no significant difference between diversion types (orthotopic neobladder, continent cutaneous diversion, and ileal conduit)^[11]. On the other hand, other studies found UTIs to be more frequent in orthotopic neobladder than in heterotopic

diversions^[12,13].

Urinary leakage

Ileal conduit ureteroileal anastomosis leak occurs in 2%-5.5% of the patients in the short term. Urethral anastomotic leaks in orthotopic neobladders are more frequent, reaching a rate of 25% in the first 90 days. In a case series by Nazmy *et al.*^[2], of the RARCs with neobladder, 25.3% had urethral leaks but most were minor and only 7.7% had a leak requiring catheterization, in line with previous reported rates. Treatment is most frequently conservative^[2].

Late post-operative complications

As studies in urinary diversion complications usually focus on early complications due to the high early mortality of the underlying cancer, with cancer-specific survival rates of 66% at 5 years^[14], high-quality information on long-term complications is sparse. Long-term complications are most frequently related to the urinary diversion itself than the extirpative radical cystectomy. A large series of conduit patients (1057 patients) reported a high long-term complication rate of almost 80% at 20 years but a low reintervention rate of 6%^[15]. In their series of about 1000 patients with ileal neobladder followed over 25 years, Hautmann *et al.*^[16] report a long-term complication rate of 40.8%, mostly diversion-related, with 3 neobladder-related deaths. They underline the importance of standardized reporting of long-term complications in a time-dependent matter, explaining that only this way investigators can stop underrepresenting late complications since the number of patients decreases with time^[16]. However, studies with this methodology are still lacking, so most of the following complication rates are still calculated on a non-time-dependent matter.

Renal failure

New onset of renal failure occurs in 19% at a median of 2.3 years, with 2.5% progressing to renal replacement therapy at a median of 8.4 years^[15]. This is intimately related to ureteroenteric stenosis causing hydronephrosis, which will be reviewed below, and also to chronic infection and reflux of infected urine. It remains to be clarified if this loss of renal function is greater than the expected age-related deterioration. Careful follow-up is needed.

Metabolic abnormalities

Metabolic complications are linked to the intestinal shortening, the bowel segment resected and the absorptive properties of the conduit or neobladder intestinal mucosa. Acid-base disorders, vitamin deficiencies and electrolyte disturbances are consistently reported in the literature. The most frequent pH disturbance is metabolic hyperchloremic acidosis due to chloride absorption and bicarbonate excretion, especially if a colonic segment is used. Vitamin B₁₂ deficiency is also expected, as this vitamin is absorbed in the terminal ileum, a segment frequently resected to use both in conduits and neobladders. This hypovitaminosis is mainly asymptomatic but can evolve to megaloblastic anemia, neuropathy, glossitis, and other diseases after the body's stores are depleted, which usually last 3-5 years^[17].

A large series of intestinal conduit diversion patients described 10.2% of metabolic acidosis requiring alkalinizing treatment and 3% of vitamin B₁₂ deficiency occurring after a median of 9 years after surgery^[15]. In continent diversions, long-term metabolic abnormalities can occur in as high as 50% of the patients^[1]. In a neobladder sample, metabolic acidosis was diagnosed in the early post-operative period but 33% of the patients needed alkalinizing therapy for longer than 1 year and 1% of the patients were rehospitalized due to the acid-base imbalance^[16].

Acidosis may be managed with alkalinizing treatment with sodium bicarbonate and vitamin deficiency with oral or parenteral supplementation^[15-17].

UTI

Risk factors for UTIs are incomplete emptying of urinary pouch (as residual urine is an infectious focus), intermittent catheterization or stenosis of the stoma or ureterointestinal anastomosis. Bacteriuria is common in these patients, but UTIs and urosepsis are not, so there is no need for prolonged suppressive antibiotic therapy. Although less frequent than in the early post-operative period, UTI in this setting should also be treated with a short course of antibiotics^[16].

Urolithiasis

The bowel epithelium, incomplete emptying of reservoirs with urinary stasis, foreign materials like staples, and chronic bacterial colonization or UTIs all contribute to stone formation, not uncommon in these patients^[17]. These stones are mostly infectious and mixed, with metabolic stones being less frequent, particularly if only reservoir stones are considered^[18].

Regarding the role of staples in stone formation, Muto *et al.*^[19] reviewed their series of stapled neobladders and report a global stone rate of 4.6%, with a risk of stone formation of 4.5%, 6.5%, 8.5%, and 10% at 5, 10, 15, and 20 years, respectively. They highlight the role of synchronous risk factors such as outlet obstruction and UTI in these patients and note that when they treated the stones endoscopically, the stapled lines were usually completely covered by mucosa^[19].

A study on conduit recipients reported a stone rate of 15.3% at a median of 2.5 years, more frequently in the upper urinary tract than in the conduit; less than 20% required treatment^[15]. Marien *et al.*^[18] studied 99 patients with urolithiasis after urinary diversion (not exclusively oncologic patients) and report an equal rate of upper and lower urinary tract stones, including 15 patients with both. The rates of urolithiasis in a recent meta-analysis were 3.5% for ileal conduits and 6.4% for neobladders, with a statistically significant difference^[20]. Treatment options include all classical options for urolithiasis treatment, but endourological procedures and external lithotripsy are preferred^[15].

Ureteroenteric stricture

All but the cutaneous ureterostomy diversion involve uretero-enteric anastomoses. There are multiple techniques for anastomosing the ureters to the bowel, either refluxing or nonrefluxing.

The stricture of this anastomosis is a well-recognized complication with its serious consequences being the deterioration of the glomerular filtration rate with loss of kidney function. The rates of stenosis described in the literature range from 1.3% to 10%, occurring predominantly on the first 2 years after surgery^[2,21].

Ureteroenteric stricture can have malignant causes, but most are benign. The pathophysiology of the benign stricture formation is not fully understood but it is likely secondary to ischemia or urine leakage leading to periureteral fibrosis. Preserving the ureteral blood supply, with careful handling and minimization of electrocautery around the ureters, and the creation of tension-free anastomoses may reduce the stenosis risk. Excision of redundant ureteric length, wider anastomosis, using stents for protection and testing with saline for leaks are other recommendations that can reduce the rate of this complication^[21]. The use of intraoperative indocyanine green (ICG) fluorescence to evaluate ureteric vascularity and choose the site of ureteric division may reduce the risk of stricture; this is specially used in RARC, using the camera's capabilities^[22].

After development of a stricture, the patients can complain of flank pain or present with recurrent UTIs or urinary stones. If they develop an acute obstruction, decompression with a percutaneous nephrostomy is required. Nevertheless, a significant proportion will be asymptomatic, with diagnosis of ureteroenteric stenosis after imaging exams incidentally revealing hydronephrosis or blood tests hinting a deterioration of renal function.

The open repair of the stenosis with excision of the affected segment and reimplantation of the ureter is the gold-standard treatment, with the greatest rates of long-term success (up to 80%), but it involves high technical expertise as these patients frequently have adhesions from the previous surgery. Therefore, minimally invasive options are being increasingly used.

Endourological access to the stenosis can be retrograde or antegrade through a percutaneous nephrostomy. Treatment may involve stenting, balloon dilation, or endoureterotomy (using cold knife, laser, or other devices); balloon dilation is the less effective method. These techniques have reported success rates of 4%-50%.

Although achieving less long-term patency when compared to open revision, endourological techniques have less morbidity, shorter operative times and post-operative recovery and reduced costs, what makes them an attractive option. In general, endoscopic techniques are recommended as a first-line treatment for short strictures (≤ 1 cm) and for patients who cannot stand open repair^[21,23].

Minimally invasive alternatives to open revision, such as laparoscopic and robot-assisted repair, seem to achieve similar results with less morbidity^[24,25]. All these techniques are useful in managing this frequent complication, when carefully selected.

DIVERSION SPECIFIC COMPLICATIONS

Each diversion type has its own specific complication, related not only to the construction of the diversion but also to the chosen intestinal segment. The surgical approach (open *vs.* robot-assisted and extracorporeal *vs.* intracorporeal) is not related to specific complications^[6,7].

Ileal conduit

Parastomal hernia

Parastomal hernia (PSH) definition can be clinical or radiographic, with substantial heterogeneity across studies. The largest systematic review to date, which included only retrospective observational studies, used a clinical definition of a palpable bulge at the base of stoma and a radiographic definition of a cross-sectional image evidencing protrusion of intraabdominal contents through the abdominal wall defect created to fixate the conduit. Of the total of 3170 patients submitted to radical cystectomy with ileal conduit, 529 (17.1%) developed a PSH based on those criteria. The authors point that a substantial number of PSH remains asymptomatic and are only detected in the oncologic follow-up imaging studies^[26].

Treatment of PSH may be needed to alleviate symptoms such as pain or poor fit of ostomy bags or because of more serious complications like bowel obstruction or strangulation. Conservative treatment with the use of a hernia belt is a possibility, but no studies reported outcomes related to this modality. Surgical correction for PSH is frequently avoided due to the difficulty of the technique, high morbidity, and frequent hernia recurrence. Common procedures include local repair, the use of a synthetic or biological mesh, or relocating the stoma, mainly based on general surgery literature. A technique of local repair of PSH after ileal conduit was described by Rodriguez Faba *et al.*^[27]: a ipsilateral relocation of stoma without the need of midline

incision, reducing the surgical risks. The global recurrence rates following surgical treatment of PSH in the largest systematic review were 27%-50%^[26].

Another approach to PSH is prevention. The first randomized controlled study on the prevention of PSH after ileal conduit urinary diversion following radical cystectomy has been published with promising results. The authors concluded that the addition of a prophylactic sublay mesh decreases the risk of PSH, with incidences at 24 months of 11% in the intervention group compared to 23% in the control group. There was a small increase in median intraoperative time of ~50 min and no greater risk of mesh-related complications. As an increased BMI was also associated with a higher risk of PSH in this study, the authors recommend the use of this prophylactic measure especially in obese patients. Studies with longer follow-up periods and health-economic analysis can clarify the role of the prophylactic mesh in a wider population^[28].

Conduit deformities

Conduit stricture and conduit elongation are possible complications of this diversion, poorly defined and reported in the literature. Shimko *et al.*^[15] reported conduit strictures in 2.4% of patients at a median of 9.4 years. These complications are reportedly less frequent than stomal complications.

Orthotopic neobladder

Rupture

Neobladder rupture is a rare but feared complication, possibly life-threatening. In large series of neobladder patients by Hautmann *et al.*^[16], 3 in 923 patients had neobladder rupture. Possible causes are perforation during catheterization, external trauma like car accidents, or outlet obstruction by a mucous plug. It can also happen spontaneously, for example in acutely or chronically overdistended reservoirs with wall ischemia or in patients previously submitted to pelvic irradiation. Timed micturition and post void residual volume surveillance (either with echography or catheterization) are advised in order to prevent this complication. In the event of rupture, these patients often present with an acute abdomen and need a relaparotomy to drain the urinoma and to repair the perforation or construct a substitute diversion. Alternatively, there are some descriptions of a conservative approach with neobladder catheterization, bilateral nephrostomies, and abdominal drain, in strictly selected patients with a mild presentation and hemodynamic stability^[29].

Fistula

Urinary diversion-enteric fistula is a rare complication, occurring in less than 2% of the patients submitted to radical cystectomy. Few studies are published on this complication and most involve neobladder patients. The most common and characteristic presentation is fecaluria, but pneumaturia and recurrent UTIs are other complaints. Diagnostic investigation with a CT usually shows air in the intestinal reservoir; if oral contrast is administered, it can appear in the urinary system. Msezane *et al.*^[30] report the location of the fistula to be more frequently from the small bowel anastomosis to the anterior neobladder wall. Small fistulas can be treated conservatively, with total parenteral nutrition, bladder drainage and treatment of sepsis, if present. For bigger fistulas or in cases of conservative treatment failure, open repair is the gold standard.

In women submitted to vaginal-sparing radical cystectomy with orthotopic neobladder creation, a neobladder-vaginal fistula can form in 2.7%-8.8%, result of a much thinner neobladder wall^[31]. Injury to the vaginal wall during dissection of the posterior bladder wall and urethra is an important risk factor, in which case conversion to other urinary diversion may be advisable^[32]. Omental flap interposition between the neobladder and the vaginal stump during cystectomy or avoidance of overlapping suture lines are

preventive measures, although it may not always prevent fistulization^[31].

These patients present with urinary incontinence and the fistula can be confirmed by cystoscopy or voiding cystography. Conservative management is invariably unsuccessful. The initial treatment option is a multilayered fistula closure via a transvaginal approach^[31]; interposition with a Martius flap is an alternative, particularly important in recurrent fistulas^[33,34]. In case of failure of the transvaginal approach, a transabdominal approach or conversion to a cutaneous diversion may be needed^[31].

Hypercontinence

Failure to empty the neobladder and urinary retention is much more frequent in women than in men. Neobladder patients with emptying failure can present with urinary retention but also with recurrent UTIs, hydronephrosis, or overflow incontinence.

The risk of retention increases with time, and emptying failure rates range from 4% to 8% in men and 24% to 62.5% in women^[35,36].

The cause of urinary retention in female neobladder recipients is still controversial. The literature ascribes the retention in women more to mechanical factors than functional or neurogenic ones; an explanation given for this chronic retention is a urethral “kinking” by prolapse of the vaginal stump with herniation of the posterior pouch through the anterior vaginal wall, due to lack of proper back support. Ali-El-Dein *et al.*^[37] focused on this matter and defined chronic retention by a post-void residue of 20% of mean maximal pouch capacity (approximately 100 mL). They reported a chronic retention rate of 16% and provide some surgical modifications to prevent this complication: reinforcing the back support of the neobladder with an omental flap, suspending the vaginal wall by the round ligaments or peritoneum, or suspending the pouch ventrally to the back of the rectus muscle^[37]. Genital sparing surgery, when possible, is another alternative. Other possible causes are large capacity pouches due to excessive bowel segment length or even autonomic denervation of the urethra^[36].

After diagnosis of chronic retention, temporary measures involve manual reduction of the prolapse during voiding or the use of a pessary; surgical revision with ventral suspension of the pouch can also be tried^[37]. Despite that, they might need intermittent catheterization. In a study by Ahmadi *et al.*^[35], 9.5% of male patients needed at least one catheterization per day and 1 patient could not urinate without catheterization. Intermittent self-catheterization was most commonly started during the first post-operative year^[35].

Urinary retention can less frequently be due to subneovesical obstruction either by tumour recurrence, stenosis of the urethral anastomosis, or the urethra itself; the reported rates of these complications on one study were 1.1%, 1.2%, and 0.9%, respectively, and in this study all strictures were treated by endoscopy^[16]. Therefore, patients with emptying failure should undergo urethrocystoscopy to identify these possible causes.

Incontinence

Urinary incontinence is a very subjective complication. Its rates in the literature vary between daytime (7%-13%) and nighttime (14%-43%) and depend greatly on the type of questionnaire used. A more objective way of evaluating urinary incontinence is pad weight measurement, but it also lacks standardizing, and an alternative measure is the number of pads per day^[35]. This heterogeneity plus the variety of possible procedures (such as cystoprostatectomy, pelvic exenteration, vaginal-sparing techniques, and nerve-sparing) hinders the comparison of different studies^[38].

In a study by Ahmadi *et al.*^[35], self-reported rates of daily urinary leakage reached 39.7%, causing almost half the patients to need to wear at least 1 pad per day. Nocturnal leakage was even higher (54.7%) with many patients needing diapers at night. Notably, most did not report bothersome skin irritation or body odor^[35]. Daytime incontinence of 3%-43% and nighttime incontinence of 0%-42% were the rates reported in a systematic review of female cystectomized patients. Nerve sparing techniques seem to improve continence, but more studies are needed in this area^[38].

Continence rates improve over time for most patients for up to 2 years after surgery, as the neobladder capacity increases. If incontinence persists, treatment options are diverse, including anti-muscarinic agents like tolterodine, periurethral collagen injections, bulking agents, urethral slings or external artificial urinary sphincters, and even trans-obturator taping^[39,40].

CONCLUSION

Radical cystectomy with urinary diversion is undoubtedly the most difficult surgical procedure in urology. Complication rates are high in the early and late settings, with various complications described in the literature. There is an urgent need of standardizing complication reporting so different series can be comparable. This review highlighted some of the most common complications and their possible management options. Careful patient selection, thorough long-term follow-up and standardization of complication reporting are mandatory conditions to achieve successful outcomes.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and organization of the review and performed literature review: Laranjo Tinoco C, Lima E

Availability of data and materials

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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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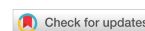
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Review

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Prevention and management of ERCP-related complications

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) and its related procedures are established as necessary and indispensable techniques in the diagnosis and treatment of bilio-pancreatic diseases. However, these procedures are associated with a high risk of complications, and caution is needed as the complications may occasionally follow a fatal course. The primary complications are pancreatitis, bleeding, perforation, and issues associated with biliary stents and lithiasis treatment. Endoscopists must perform ERCP with a strong understanding of the mechanisms of each of these complications and should be familiar with the prevention and countermeasures.

Keywords: ERCP, complications, prevention of complications, countermeasure of complications

INTRODUCTION

The complication rate of endoscopic retrograde cholangiopancreatography (ERCP)-related procedures is high among other endoscopic techniques, and complications may deteriorate into more serious conditions occasionally. Accordingly, it is necessary to be familiar with methods to prevent complications and to treat them should these occur. Here, we describe the primary complications associated with endoscopic therapies for biliary disease and discuss possible treatment approaches.



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POST-ERCP PANCREATITIS

Post-ERCP pancreatitis (PEP) can be fatal. In a systematic review that included 21 retrospective studies, the incidence rate of PEP was 3.5%, the incidence rate of severe pancreatitis was 0.4%, and the mortality rate was 0.11%^[1].

The risk factors for PEP can be patient-related or procedure-related. Patient-related risk factors include sphincter of Oddi dysfunction, female sex, history of pancreatitis, young age, non-extrahepatic bile duct dilation, non-chronic pancreatitis, and normal serum bilirubin. Procedure-related risk factors include precut sphincterotomy, pancreatic duct injection, 5 or more cannulations, pancreatic sphincterotomy, papillary balloon dilation, and endoscopic papillectomy. Furthermore, in a recent systematic review, history of PEP is proposed as a risk factor^[2]. These factors must be considered while performing ERCP and other related procedures.

Pancreatic stent placement

There are many reports on the usefulness of pancreatic stent placement to prevent PEP. Mazaki *et al.*^[3] performed a meta-analysis of 14 randomized controlled trials and reported a significant reduction in PEP incidence in the prophylactic pancreatic stent placement group with respect to the group without stent placement. The authors concluded that pancreatic stent placement was useful in the prevention of PEP^[3]. Mine *et al.*^[4] also recommended prophylactic pancreatic stent placement in patients at high risk of PEP. The stents used were spontaneous dislodgement pancreatic stents^[4]. Regarding stent diameters, Zolotarevsky *et al.*^[5] confirmed that the placement success rate was higher with 5Fr than that with 3Fr stents, but there was no difference in the PEP prevention effects according to the size. Because a 3Fr stent requires a 0.018-inch guidewire, manipulations may be difficult and fluoroscopy results can be poor. With a 5Fr stent, the procedure can be performed with a small guide wire and placement takes less time. Therefore, 5Fr pancreatic stents are recommended^[6]. That said, adverse events related to pancreatic stents may occur, including damage to the pancreatic duct, inward migration of the stent, and pancreatitis due to stent occlusion^[7-8]. Because there is a risk of pancreatitis onset if the pancreatic stent does not spontaneously dislodge, the stent should be endoscopically removed in such cases^[9]. Of note, approaching the pancreatic duct again to place a pancreatic stent after treating the bile duct may actually increase the risk of PEP. Pancreatic stents should be aggressively placed if a guide wire is located in the pancreatic duct, such as during pancreatic duct injection of a contrast or pancreatic guide wire cannulation. However, when only the bile duct is treated, whether to place pancreatic stents should be considered on a case-by-case basis.

Wire-guided cannulation

Because the injection of a contrast agent into the pancreatic duct may be a risk factor for PEP, wire-guided cannulation (WGC), wherein a guide wire is cannulated into the bile duct without injection of a contrast agent, was developed. It is reported to be associated with lower PEP incidence compared to conventional contrast-enhanced methods and increased rate of deep bile duct cannulation^[10]. It is widely used in the Western countries as the standard procedure for bile duct cannulation. Meanwhile, a multicenter, joint randomized controlled trial in Japan showed no significant difference in the PEP incidence and deep bile duct cannulation rate between the WGC method and conventional contrast-enhanced method^[11]. However, further studies will be needed in the future on the selection of cases indicated for the WGC method. If the bile duct cannulation is challenging, we recommend that a prompt switch to another method to help prevent the onset of PEP.

ERCP-ASSOCIATED BLEEDING

Bleeding is seldom encountered in normal ERCP cases. Papillary treatments such as endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), and endoscopic papillectomy are the primary causes of bleeding. Although a majority of the cases of bleeding are minor and bleeding may spontaneously stop during treatment^[1], it sometimes may obscure the field of view. Patient-related risk factors of post-EST bleeding include the presence of coagulopathy, undergoing anticoagulant therapy within 3 days of ERCP, and active cholangitis^[12]. Anticoagulants and antiplatelet agents (APA) are associated with post-ERCP bleeding, and the American Society for Gastrointestinal Endoscopy suggests refraining from APA when undergoing ERCP^[13]. Alternatively, aspirin use is considered safe and has not been reported to increase the risk of post-ERCP bleeding^[14-16]. The association between thienopyridine (i.e., ticlopidine, clopidogrel, and prasugrel) and bleeding risk has not been sufficiently studied. However, it is recommended that administration of these drugs should be halted for at least 5-7 days and instead, aspirin should be administered when conducting EST, which is a high-risk procedure^[13].

In regard to the angle of EST, the direction from 11 to 12 o'clock is thought to be associated with the lowest perforation and bleeding risk. In the event of non-arterial bleeding, spraying epinephrine solution is useful. Balloon tamponade of the sphincterotomy site is also used to stop the bleeding^[17] [Figure 1]. A randomized trial of 120 patients found that prophylactic injection of hypertonic saline-epinephrine proximal to the papilla significantly reduced the risk of post-EST bleeding^[18]. Hypertonic saline-epinephrine is also useful for treating intraprocedural bleeding. Thermal therapies such as high-frequency coagulation hemostasis [Figure 2] and argon plasma coagulation, cauterization hemostasis, or use of clips (hemoclips) [Figure 3] are useful. If placement of hemoclips by using a duodenoscope is challenging, use of a forward-viewing endoscope with a cap may be facilitated^[19]. In either case, it is important to avoid the pancreatic orifice during thermal and mechanical applications. In case of bleeding from the papilla into the bile duct, it may not be possible to implement any of the aforementioned hemostatic techniques, and in such cases, a covered metallic stent may be effective for achieving hemostasis^[20]. In addition, interventional radiology should be considered when endoscopic hemostasis is difficult. The rate of successful bleeding control with interventional radiology has been reported to be 83%-91% and should thus be considered prior to surgery^[21-22]. In such cases, clipping at the bleeding site is a useful marker of the culprit vessel.

ERCP-ASSOCIATED PERFORATION

Treatment approaches differ according to the perforation site. According to one study, perforations can be divided into three types: guide wire perforation, papillary perforation, and duodenal perforation^[23]. An alternate classification has also been proposed: duodenal perforation, papillary perforation, bile duct perforation, and retroperitoneal emphysema^[24]. A majority of bile duct perforations and papillary perforations can be treated conservatively; however, most duodenal perforations require surgical treatment. Because treatment approaches differ according to the perforation site, it is important to start immediate treatment after having made a definite diagnosis in the event that a perforation has occurred.

Papillary perforation, bile duct perforation

Papillary perforation may also occur during EST, EPBD, and endoscopic papillary large balloon dilation (EPLBD), as well as during insertion of biopsy forceps and basket forceps into the common bile duct after EST and EPLBD. EST should be performed carefully so that incision is not made in an improper direction or an unnecessarily large incision is avoided. When perforation is suspected in ERCP, it is preferable to perform ERCP using CO₂ gas, so that the retroperitoneal space would not be widened due to pressure from the transport gas. It is important to perform sufficient bile duct drainage and minimize the collection of intestinal juices and infection in the retroperitoneal space; this facilitates conservative treatment. For

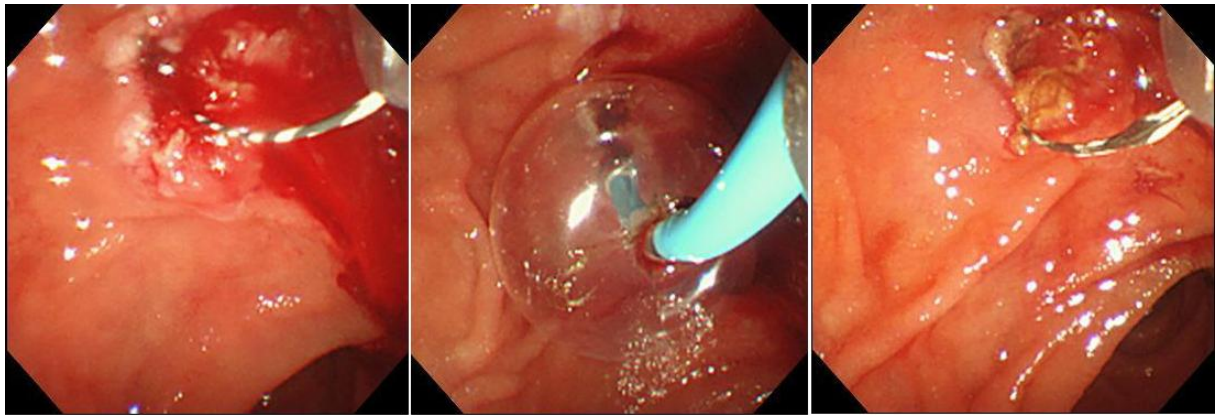


Figure 1. Hemostasis performed by balloon pressure hemostasis for bleeding after endoscopic sphincterotomy.

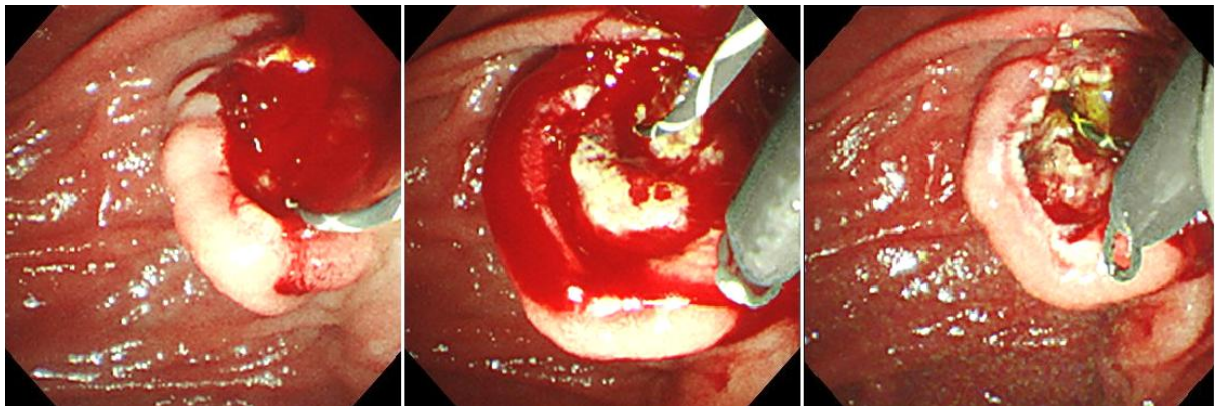


Figure 2. Hemostasis performed by Hemoclip for a vascular bleeding after endoscopic sphincterotomy.

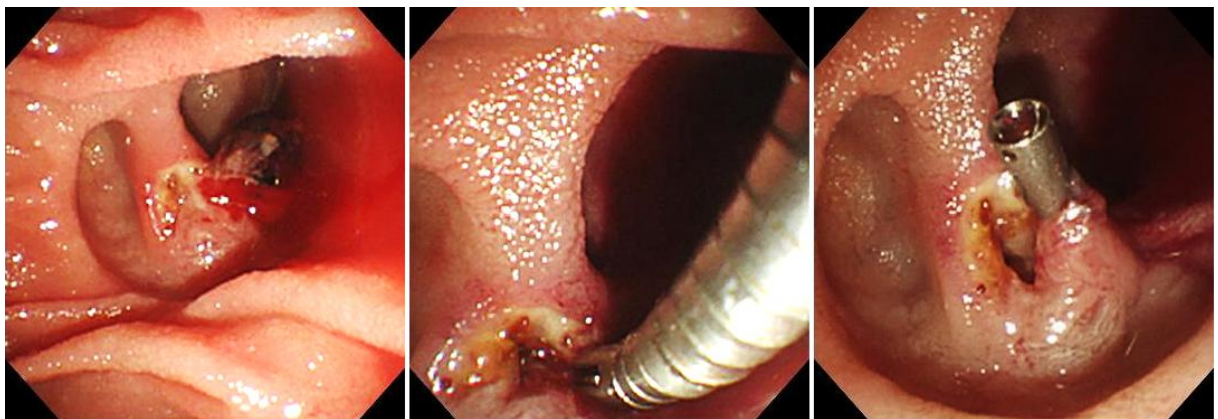


Figure 3. Coagulation hemostasis performed by Snare-tip for bleeding after endoscopic sphincterotomy.

papillary perforations, endoscopic nasobiliary drainage or biliary stent should be placed in the common bile duct, and the closure of the perforation should be attempted using clip forceps. Thereafter, a gastric tube should be placed, while conservative observation is performed by administering antibiotics and proton pump inhibitors. A papillary perforation has been treated conservatively with compression closure by

placing a covered metallic stent^[25] [Figure 4]. Similar actions are performed in cases of papillary or bile duct perforation by a basket forceps that is associated with common bile duct stone removal. Generally, papillary perforations and bile duct perforations are caused by treatment devices, and they can usually be alleviated by bile duct drainage, gastric tube placement, and antibiotics administration^[26]. Post-ERCP, free air should be checked for, as well as fluid collection in the retroperitoneal space and ascites on an abdominal computed tomography (CT). Surgical treatment should be considered in cases where progression of symptoms such as fever and abdominal pain, elevated inflammatory response, and an increasing trend of retroperitoneal space fluid collection and ascites on CT are observed.

Duodenal perforation

Duodenal perforation occurs normally during scope insertion into the descending duodenum and stretching procedures. Since adhesions of the duodenum due to previous abdominal surgeries or cancer invasion may cause perforations, it is important to perform ERCP with an awareness of preventing duodenal perforation, such as performing ERCP without the stretching procedure. Clip closure with a clip can be performed for duodenal perforations with additional conservative treatment^[27]. Recently, the efficacy of over-the-scope clip for perforations during pancreaticobiliary endoscopy has been reported^[28]. Duodenal perforations are usually direct injuries of the intestinal wall due to endoscopy and have large perforation hole. Hence, careful consideration is required for the indication of endoscopic closure, and surgical closure of the injury should be considered first.

ERCP-RELATED TREATMENT ISSUES

Acute cholangitis

Sepsis may occur after emergency ERCP for acute obstructive septic cholangitis. To avoid an increase in the pressure within the bile duct, ERCP should be performed initially with a small amount of contrast agent and then with endoscopic nasobiliary drainage or biliary stent drainage alone. Lithiasis treatment should be performed following cholangitis control.

Furthermore, during drainage for malignant hilar obstruction, it is preferable to not perform bile duct contrast imaging on the other side of the bile duct expected for drainage, so as to prevent cholangitis^[29]. It is important to preoperatively determine the bile duct expected for drainage in advance by CT or magnetic resonance cholangiopancreatography. Although there are reports that unilateral drainage has lower risk for cholangitis than bilateral drainage^[30-31], examination on a case-by-case basis is necessary as the obstruction state will differ depending on the case.

Acute cholecystitis

Acute cholecystitis is a complication that may occur after metallic stent placement^[32-33]. The risk is particularly high in cases where a tumor extends to the cystic duct and where the cystic duct is obstructed by a covered metallic stent. Furthermore, the risk has been reported with the presence of stones in the gallbladder and the filling of the gallbladder with contrast during the examination^[14]; adequate attention should be taken to prevent excessive contrast. If there is no improvement with conservative therapy, percutaneous transhepatic gallbladder aspiration or percutaneous transhepatic gallbladder drainage should be considered. In the case of cholecystitis due to a covered metallic stent, removal of the stent and replacing with a plastic stent or uncovered metallic stent should be considered.

Stent migration

Migration of plastic stents into the bile duct has been observed. Proximal stent migration was reported in approximately 5% of cases in an initial report^[34]. Malignant strictures, larger diameter stents, and shorter stents were significantly associated with proximal biliary stent migration^[34]. In case of proximal migration, a

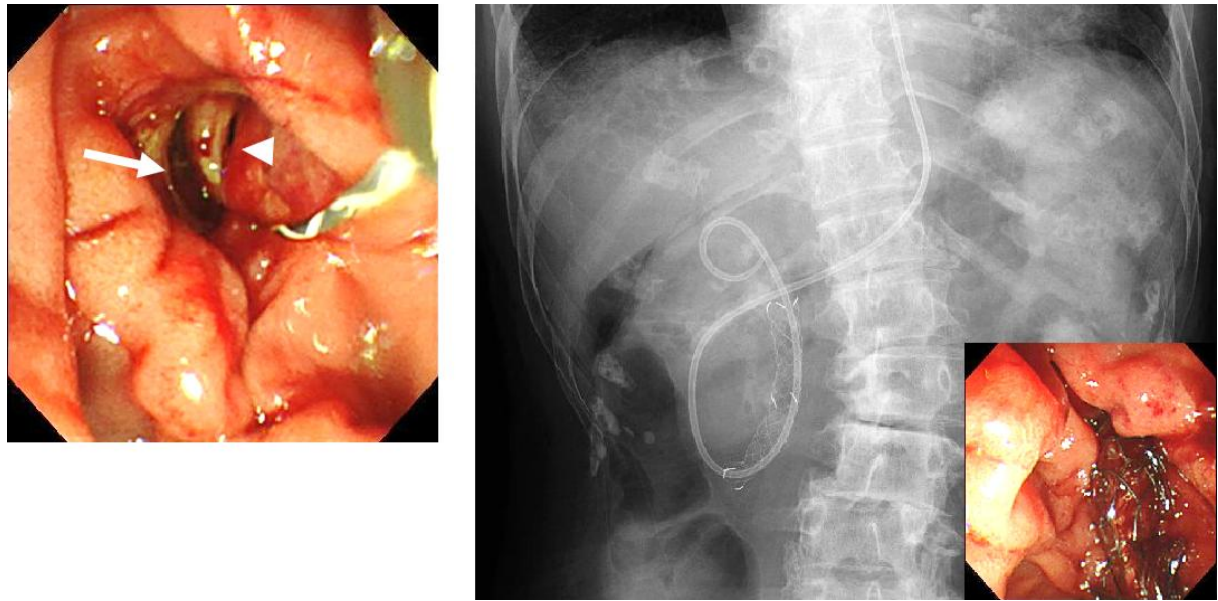


Figure 4. Case of papillary perforation after endoscopic sphincterotomy. The bile duct (arrowhead) and the perforation (arrow) were confirmed. Covered metallic stent was placed for the purpose of compression closure, and endoscopic nasobiliary drainage was performed. It subsequently conservatively alleviated the complication, and surgical treatment was avoided.

guide wire could be passed through the inside of the plastic stent, and the stent could be removed with a Soehendra® Stent Retriever or a balloon catheter [Figure 5]. In cases where a guide wire could not be passed through the inside of the stent, the distal end could be grasped with a basket forceps, grasping forceps, or polypectomy snare, and the stent could recover under fluoroscopic guidance.

Bile duct bleeding

Bleeding from the tumor may occur in malignant bile duct stricture. Although this bleeding usually stops spontaneously, a covered metallic stent could be placed and pressure hemostasis could be performed in cases where bleeding from the tumor is continuous and the anemia progresses (video). In cases where hemostasis is still difficult to achieve, hemostasis by interventional radiology should be considered.

LITHIASIS REMOVAL-ASSOCIATED ISSUES

When grasping a common bile duct stone with a basket forceps, crushing the stone may be difficult due to its size or hardness, and the basket may be impossible to pull out from the papilla, thereby becoming strangulated.

When the papillary incision is small, the outside sheath of the basket forceps can be pulled off, leaving just the wire. Then, the papilla can be further dilated using a dilation balloon catheter, and it can then be removed along with the stone. If that is difficult, an endotripter may be useful. The handle of the basket catheter is cut off, and thereafter, the metal sheath of the endotripter is passed after covering the wire of the basket. In through-the-scope type thin endotripters, this action is possible without removing the scope, but for endotripters that are not through-the-scope type, the scope should be removed, and the metal sheath passed under X-ray fluoroscopic guidance. Once the metal sheath has been passed up to the basket impaction, the wire can be fixed onto the handle of the endotripter, and the stone can be crushed releasing the impaction [Figure 6]. Because basket impaction is a serious complication, it is important to always have an endotripter ready while performing lithiasis treatment.

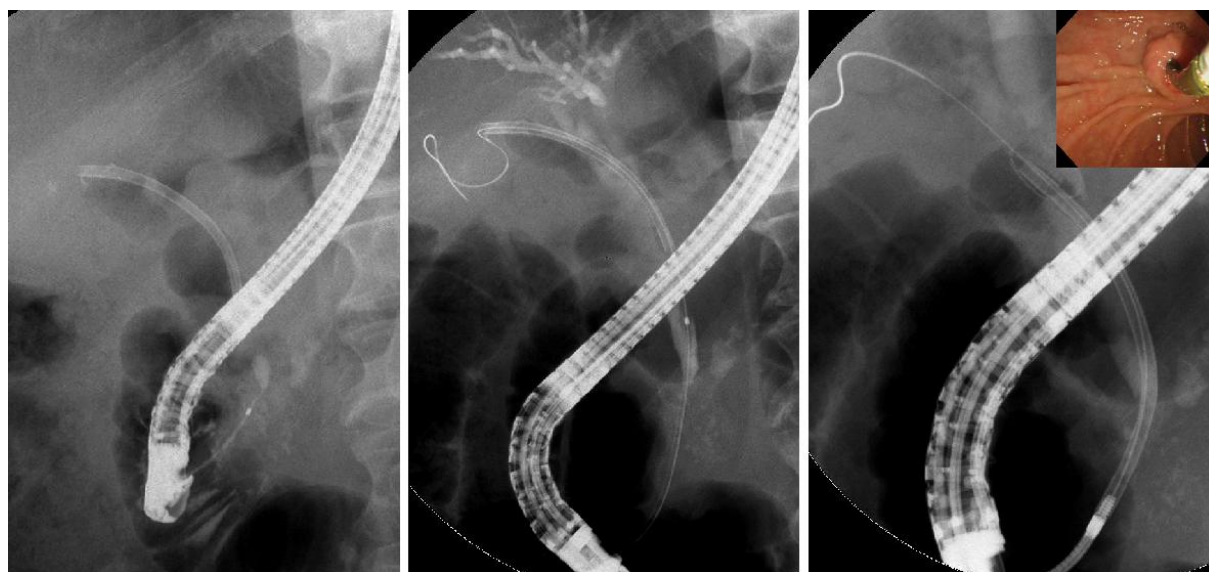


Figure 5. A bile duct plastic stent migrated into the bile duct. A contrast-enhanced cannula was guided under fluoroscopic guidance to the distal end of the plastic stent, and then a guide wire passed through the inside of the plastic stent. A Soehendra® Stent Retriever was covered over the guide wire and guided under fluoroscopic guidance, the end locked onto the stent, and then withdrawn to the duodenum under fluoroscopic guidance.



Figure 6. Although mechanical lithotripsy was attempted on a giant stone, the stone was hard and damaged the wire, and the basket was impacted. The impaction was released using an endotripter, and a tube stent was placed.

If the methods described above fail, then the impaction can be released by crushing the stone with extracorporeal shock wave lithotripsy or with electrohydraulic lithotripsy under peroral cholangioscopy.

CONCLUSION

ERCP-related procedures are important and indispensable techniques for the diagnosis and treatment of bilio-pancreatic diseases. There are many serious complications associated with ERCP-related procedures. Endoscopists must approach ERCP with an appropriate understanding of the complications and should be familiar with the prevention and countermeasures.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Ito K, Igarashi Y

Performed data acquisition, as well as provided administrative, technical, and material support: Takuma K, Hara S, Igarashi Y

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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Case Report

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Laparo-endoscopic single site hysterectomy in renal transplant women using conventional laparoscopic instruments

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Abstract

Kidney transplant recipients are at a higher risk of developing cancers as compared to the general population. This is of concern when it comes to gynaecological pathologies because the transplanted kidney lies in the pelvic region, in close proximity to the diseased organ. The successful use of laparo-endoscopic single site surgery with conventional laparoscopic instruments for total hysterectomy and bilateral salpingo-oophorectomy in three patients with prior renal transplantation is reported.

Keywords: Laparo-endoscopic single site surgery, hysterectomy, renal transplant, laparoscopy, ovarian tumour, endometrial cancer

INTRODUCTION

The prevalence and incidence of end-stage renal disease (ESRD) has been increasing across the world. It is expected that around 1.5% of people with an estimated glomerular filtration rate of 15-60 mL/min/1.73 m² transition to ESRD every year^[1]. The standard of care for patients with ESRD is either dialysis or kidney transplantation. Numerous studies have shown that patient survival is significantly higher with kidney transplantation than with dialysis. Moreover, with the use of better immunosuppression and improved surgical techniques, graft and patient survival after kidney transplantation have improved over the years^[2,3].



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However, it is known that incidence of cancer is higher in transplant recipients than in patients undergoing dialysis for ESRD. It has been hypothesised that this could be attributed to the immunosuppressants regime transplant recipients received^[4].

This case report describes three cases of gynaecologic pathologies in kidney transplant recipients and the use of laparo-endoscopic single site surgery (LESS) to perform a total hysterectomy and bilateral salpingo-oophorectomy (THBSO). In our literature review, only Zhang and Li^[5] previously described the use of LESS for THBSO in kidney transplant recipients, but there was minimal information on the type of instruments used and the management of these patients perioperatively. Therefore, to our best knowledge, performing LESS using homemade gloves and conventional laparoscopic instruments in renal transplant recipients has never been described before.

CASE REPORT

Case # 1

A 61-year-old female with a body mass index (BMI) of 22.5, who had one child delivered through normal vaginal delivery, presented with significant post-menopausal bleeding of one week duration requiring admission and blood transfusion in view of her low haemoglobin count which dropped from 12.0 to 7.7 g/dL. She has a significant past medical history of hypertension, hyperlipidaemia, ESRD secondary to hypertensive nephrosclerosis, mitral regurgitation and atrial fibrillation. She eventually had a deceased donor renal transplantation to the right iliac fossa [Figure 1A]. Her immunosuppressants were 5 mg oral prednisolone and 100 mg oral ciclosporin. She was not initiated on anti-coagulants for her recently diagnosed atrial fibrillation in view of her upcoming gynaecological surgery.

On her abdomen, there was a suprapubic transverse scar extending to the right iliac fossa. The right transplanted kidney was palpable over the right iliac fossa. On speculum, vagina and bimanual examination, the cervix appeared normal, and no obvious mass was felt.

A pelvic ultrasound was performed, which revealed a thickened endometrium of 5.7 mm, a 25 mm × 17 mm × 23 mm unilocular mass in the right adnexal region with no fluid in the Pouch of Douglas and no other masses seen in the pelvis. The IOTA score was 20%. Subsequently, histological features obtained from an endometrial biopsy suggested anovulatory cycles with disordered proliferation. At the same time, a pelvic MRI [Figure 1B] was ordered, but the malignant potential of the ovarian mass was still uncertain. Her CA125 level was 57.9. Her Papanicolaou smear yielded no abnormal finding. In view of the significant post-menopausal bleeding in the presence of a right adnexal mass, our impression was an ovarian hormone secreting tumour. Treatment options were discussed with the patient; she was keen for surgery and counselled for LESS THBSO and omental biopsy.

During the surgery, a homemade single-port system comprising of the Alexis® wound retractor (Applied Medical, CA, USA) and a 7½ surgical glove was used. After making a 2.5 cm umbilical skin incision, the wound retractor was inserted into the peritoneal cavity through the umbilicus, and the glove was fixed to the outer ring of the wound retractor. Upon making small incisions in the fingertip portions of the glove, two 5-mm trocars and one 12-mm trocar were inserted. A rigid 30°, 5 mm diameter, 45 cm long endoscope was used. The transplanted kidney was visualised at the right iliac fossa. A diagnostic laparoscopy established slightly enlarged bilateral ovarian masses without any evidence of ovarian malignancy. The right ovary measured 3.2 cm × 2 cm × 1.6 cm, while the left ovary was 4 cm × 1.5 cm × 1.5 cm. Overall, the procedure was uneventful with minimal blood loss. The final histopathological diagnosis for the patient turned out to be disordered proliferative endometrium and bilateral ovarian Sertoli-Leydig cell tumour

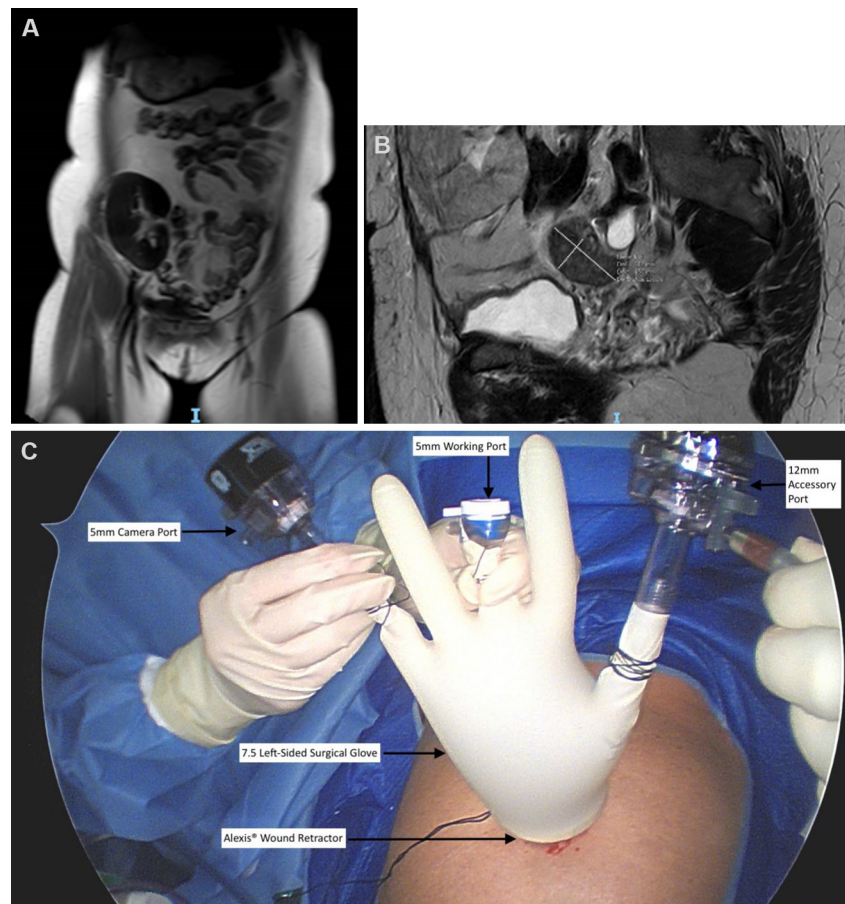


Figure 1. Pelvic MRI showing the transplanted kidney in the right iliac fossa (A). Pelvic MRI showing the right adnexal mass, measuring 25 mm × 17 mm × 23 mm (B). Labelled photo of the homemade single-port system (C).

suggestive of a benign lesion.

Postoperatively, the patient recovered well. Her renal function was monitored closely together with the renal transplant physician, and she was discharged 2 days later with a 6-day antibiotic course of 1800 mg oral clindamycin.

Case # 2

Our second patient was a 49-year-old female with a BMI of 33.2 who is married with three children. She was referred for heavy menstrual bleeding with no anaemic symptoms. Her menstrual cycles were regular, lasting 4-5 days each with heavy flow and formation of multiple small clots. Her significant past medical history includes ESRD secondary to chronic tubulointerstitial nephritis, hyperparathyroidism and post-transplant diabetes mellitus. She had previous surgeries for one termination of pregnancy, one lower segment Caesarean section, two normal vaginal deliveries, tubal ligation and two deceased donor renal transplants with both transplanted kidneys sited at the right iliac fossa [Figure 2A]. Her immunosuppressant regime was 3.5 mg everolimus, 3 mg oral tacrolimus and 5 mg oral prednisolone.

On examination, there was a suprapubic transverse scar extending to the right iliac fossa. The transplanted kidney was not palpable due to her high BMI. On speculum, vaginal and bimanual examination, the cervix was normal, and no obvious mass was felt.

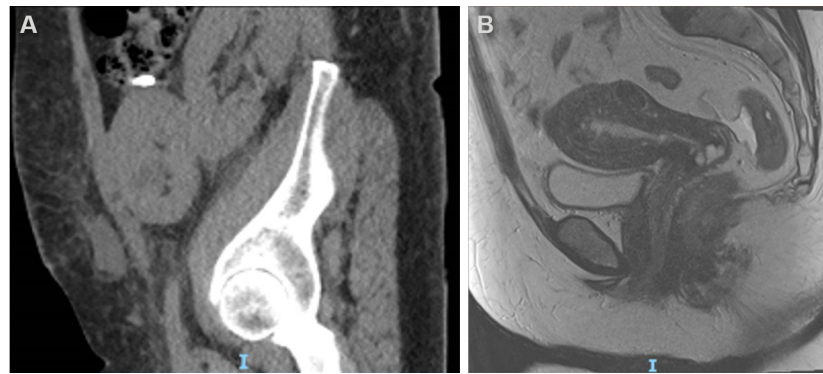


Figure 2. Pelvic sagittal view CT showing the dual kidney transplant taken immediately after the transplantation surgery (A). Pelvic sagittal view MRI showing endometrial lesion confined to the uterus (B).

A pelvic ultrasound was performed, revealing an endometrial thickness of 16.7 mm, two subserosal fibroids of 2.3 and 1.9 mm, multiple non-suspicious cysts in the left and right adnexa and a 2-cm polyp arising from the upper uterine cavity. A hysteroscopy was done for polypectomy and dilatation and curettage. The histological results of the polyp were suggestive of Grade 1 endometrioid carcinoma.

Subsequently, a pelvic MRI and thoracic and abdominal CT were ordered. The MRI results show that the cancer was confined to the endometrium without any myometrial extension or enlarged pelvic lymph nodes [Figure 2B]. Similarly, the CT scan revealed no significant enlarged lymph node elsewhere to suggest distant metastases. She was counselled for THBSO without pelvic lymph nodes dissection as it was a Grade 1 endometrioid carcinoma and, radiologically, the tumour was found to be confined to the endometrium.

The surgical technique was similar to the first case described above. However, in view of her habitus, 45-cm-long bariatric laparoscopic instruments and a 50-cm endoscope were used. The transplanted kidney was visualised at the right iliac fossa. The uterus and bilateral ovaries were normal. The procedure was uneventful and there was minimal bleeding. The final histology showed a Stage 1A Grade 1 endometrioid carcinoma of the endometrium, and there was no evidence of residual tumour.

Three days later, the patient developed thrombophlebitis which resolved with antibiotics. The patient was discharged well on Postoperative Day 6.

After discussing with our tumour board, the recommendation was to observe for disease recurrence. Currently, the patient is on follow-up with us and has been under remission for 2 years.

Case # 3

The third patient was a 78-year-old female with a BMI of 18.5 who is married with one child. She was referred for an incidental finding of a 5.5 cm × 3.6 cm left adnexal lesion with central hypodensity on pelvic CT initially performed for low back pain [Figure 3A]. She did not complain of any abdominal pain or post-menopausal bleed. Her significant past medical history includes ESRD secondary to chronic glomerulonephritis and recurrent bilateral lower limb deep vein thrombosis. She had a previous living donor kidney transplantation, open myomectomy and laparoscopic cholecystectomy. Her current medications include 8 mg prednisolone, 25 mg azathioprine, 75 mg dipyridamole and 2 mg warfarin.

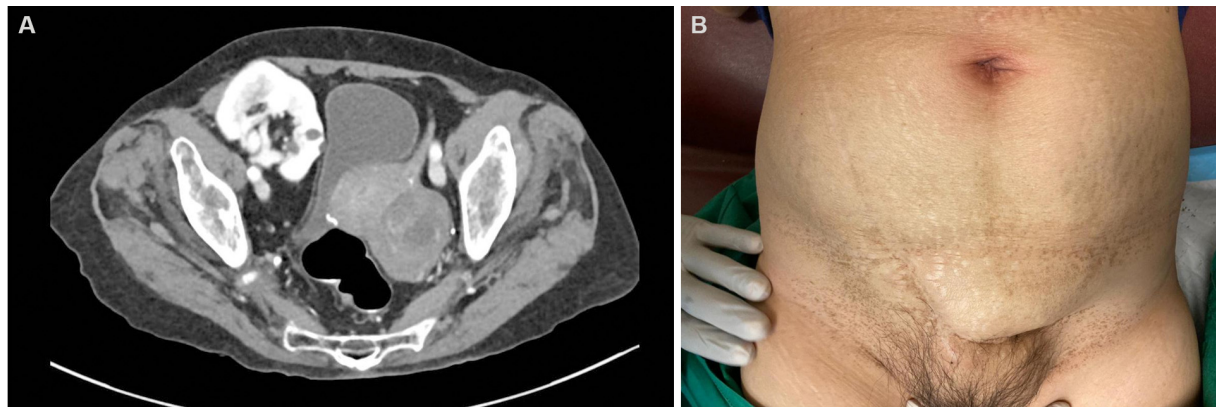


Figure 3. CT Pelvis Axial View showing the left adnexal mass and the transplanted kidney in the right iliac fossa (A). PAbdomen showing suprapubic transverse scar extending to the right iliac fossa (B).

On examination, there was a suprapubic transverse scar extending to the right iliac fossa [Figure 3B]. The right transplanted kidney was palpable over the right iliac fossa. The cervix appeared normal, and no obvious mass was felt on bimanual examination.

Pelvic ultrasound revealed a 6.0 cm × 5.0 cm × 3.5 cm multiloculated cystic mass in the left adnexal region. Colour Doppler showed mild vascularity within the mass. No ascites or other masses were noted. Tumour markers CA125 and CEA were raised to 71.8 and 11.6, respectively. The IOTA and RMI score were 6.8% and 646, respectively, suggesting a high risk of malignancy.

In view of the risk of malignancy and her immunosuppressed state, LESS THBSO was advised, and the patient was keen for the surgery.

Preoperatively, warfarin and dipyridamole were stopped 5 and 2 days prior to surgery, respectively. PT was 10.5, aPTT was 28.2 and INR was 1.0. Her preoperative Hb was 11.2. The surgical technique was similar to the first case as described above. The procedure was uneventful and there was minimal bleeding (20 mL). The final histology reported a left ovarian mucinous cystadenoma.

Postoperatively, the patient recovered well and was started on clexane by the haematologist. She was discharged on Postoperative Day 3. Currently, she is on follow-up with the gynaecological oncologist.

DISCUSSION

Performing a hysterectomy with bilateral salpingo-oophorectomy on a renal transplant recipient is not without its challenge. In a paper written by Heisler regarding hysterectomy in women who have undergone renal transplantation, it is reported that 41.4% ($n = 58$) of these patients experience postoperative complications, the most common being wound infection and bleeding requiring blood transfusion. Such complications were seen mainly in open hysterectomy^[6]. This was much higher in comparison to healthy women, in whom the figures are at an estimated 3%-22%. In the following paragraphs, we elaborate on the unique challenges faced during the operative care of kidney transplant recipients.

Bleeding requiring blood transfusion was reported as a common complication of hysterectomy in renal transplant recipients. This was because open hysterectomy was performed and many of these patients were on antithrombotic therapy^[6]. In our first and second cases, the patients were not on these medications. In

the last case, even though the patient was taking anti-coagulants and anti-thrombotics, intraoperative bleeding was minimal (100 cc), possibly reduced by the use of a laparoscopic approach.

Advances in operative techniques were also able to reduce the risk of intraoperative and postoperative complications in these group of patients. Previously, open laparotomy was the standard approach to performing hysterectomy. However, in recent years, laparoscopy became the more popular choice. Advantages of laparoscopy over laparotomy include shorter hospital stay, decreased adhesion formation and reduced incidence of fever, wound infection, urinary tract infection and pneumonia^[7,8]. This is especially beneficial in renal transplant recipients because infection is the most common complication of abdominal hysterectomy^[6]. While it was reported that the incidence of bladder injury is higher in laparoscopic hysterectomies, this risk can be mitigated when it is performed by an experienced surgeon^[8].

There are multiple advantages to performing LESS. It leads to a decrease in the risk of visceral and vascular injury related to multiple incisions and trocar placements. Furthermore, the umbilical incision for port placement in LESS is hardly noticeable after healing and offers superior cosmetic results. However, we acknowledge that this may be less important in renal transplant recipients since they already have a large kidney transplant scar. As there is only one entry site, there is also a reduction in postoperative wound infection, hernia formation and elimination of multiple trocar site closures. In addition, LESS is associated with good pain control and lower analgesic requirements, which in turn enhances the recovery of patients^[9,10]. Overall, LESS has been shown to reduce operative and perioperative complications.

Our surgeon also used a homemade single-port system which accommodates the insertion of various types and sizes of laparoscopic devices, while the elasticity of the glove finger facilitates the retrieval of specimens. The greatest advantage of a homemade port is its cost effectiveness for the patient, as standard, instead of articulated, instruments are utilised. This is feasible because the elasticity of the homemade port coupled with the thin, stretchable umbilical fascia maintains the triangulation, ease of manoeuvre and coordination of the instruments.

A technically challenging aspect of performing hysterectomy in renal transplant patients is to avoid damage to the allograft organ intraoperatively since the surgical field is in the pelvic region where the transplanted kidney is sited. Using LESS is safe because the trocar is only placed at the umbilicus, while a conventional laparoscopy requires a trocar to be inserted at the ipsilateral lower quadrant of the allograft organ, risking injury to it. Although the risk can be reduced in a conventional laparoscopy by placing the trocar more medially in such instances, attention has to be given to identify the inferior epigastric vessels before placing this port^[3]. Similarly, placing the trocar at a higher position may make the surgery less ergonomic for the surgeon. This renders a single, umbilical port placement safer and more ideal.

Moreover, there is a risk of injury to the urinary bladder during laparoscopic gynaecological surgery, attributed to either the entry process (e.g., suprapubic port insertion) or due to its close proximity with the operating field (e.g., hysterectomy). A previous meta-analysis reported that bladder injury rates range from 0.02% to 8.3%, making it the most common viscera damaged in conventional laparoscopic pelvic surgery^[11]. Renal transplant recipients undergoing conventional laparoscopy may have an even higher risk of bladder injury. During renal transplantation, the bladder is lifted supero-anteriorly to allow transplantation of the ureter to the dome of the bladder. Thus, suprapubic port insertion carries an increased risk of bladder injury due to its relatively higher position. While high port placement at the level of or above the umbilicus can be used in place of a suprapubic port, such placements are less ergonomic for the surgeon. On the other hand, entering the peritoneal cavity through a single umbilical incision in LESS minimises the risk of such port-

related bladder injury.

Retroperitoneal single-port laparoscopic hysterectomies (SP-rH) have been performed to identify the ureter and internal iliac artery, followed by ligation of the uterine artery where it originates from the internal iliac artery. SP-rH can result in less intraoperative bleeding and a decreased risk of ureteral damage^[12]. However, in patients with renal transplantation, the retroperitoneal approach can be challenging due to anatomical distortions. Furthermore, the major blood vessel supplying the kidney is derived from the external iliac vessels, and inadvertent injury to these vessels using the retroperitoneal approach may affect the function of the allograft kidney. At the same time, identifying the ureter of the allograft kidney may have limited benefit as it is transplanted to the dome of the bladder which is away from the surgical site.

Another obstacle is the high BMI of our second patient in addition to possible adhesions from her previous Caesarean section. Such a patient profile may make LESS more technically challenging and less attractive to surgeons. Some potential issues during the procedure include visual limitations and difficulty in obtaining good triangulation without collisions between instruments. However, in our experience, LESS can still be effectively performed. To improve mobility during the procedure, our surgeon used bariatric laparoscopic instruments and a 50-cm telescope. Additional surgical steps were also performed as the floppy bladder obstructed the view of the vaginal wall. Our surgeon used prolene 2-0 to suspend the uterovesical fold to the anterior abdominal wall in order to lift up the bladder. As a result, the vaginal wall can be easily visualised, which helps facilitate closure of the vaginal wall.

In conclusion, performing a LESS THBSO in renal transplant recipients using conventional laparoscopic instruments provides safe and effective outcomes which are comparable to conventional laparoscopy in the case reports described. There can be clear advantages to performing LESS when appropriate cases are selected, when it is performed by a surgeon experienced in minimally invasive surgery and when a multi-disciplinary team is involved in optimising the care of the patient.

DECLARATIONS

Authors' contributions

Performed data acquisition and writing of report: Goh WA, Tan EMX

Made contributions to conception of the study, editing and review of the report: Nadarajah 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

A written informed consent for publication was obtained from all participants.

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Opinion

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Robotic-assisted approach for complex inguinal hernias

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Abstract

Laparoscopic inguinal hernia repair was introduced in the early nineties as a minimally invasive alternative to the classic Lichtenstein repair. Over the decades, minimally invasive approaches have demonstrated both postoperative benefits and easy replicability. Robotic inguinal hernia repair has been shown as a safe alternative to laparoscopic repair. Furthermore, due to technical difficulties, complex inguinal hernia repairs (scrotal hernias, incarcerated hernias, recurrent hernias, mesh removal, and previous pelvic surgery) are a relative contraindication for laparoscopic repairs. In this article, we highlight the advantages of the robotic approach for complex cases of inguinal hernia.

Keywords: Robotic surgery, inguinal hernia, abdominal wall, minimally invasive surgical procedures

INTRODUCTION

Laparoscopic inguinal hernia repair was introduced in the early nineties as a minimally invasive alternative to the classic Lichtenstein repair^[1]. Over the next decades, two different minimally invasive approaches have been extensively published: totally extraperitoneal repair (TEP) and transabdominal preperitoneal repair (TAPP), demonstrating both postoperative benefits and easy replicability^[2-4]. Recently, minimally invasive surgery (MIS) has become the gold standard approach for bilateral inguinal hernia repair and has also been suggested for primary and recurrent unilateral inguinal hernias when expertise is present^[5]. With the



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advancing technology and progressing MIS, surgeons are utilizing robotic platforms to perform minimally invasive hernia repairs following the same technical principles. This approach has been changing surgeons' and patients' experiences.

Robotic inguinal hernia repair has been shown as a safe alternative to laparoscopic repair by studies from Kudsi *et al.*^[6], Escobar Dominguez *et al.*^[7], and Tam *et al.*^[8]. The robotic approach follows the same technical principles of the laparoscopic TAPP approach. Literature review of robotic inguinal hernia repair (rIHR) is composed of many retrospective and single-institution studies with few Randomized Controlled trials and meta-analysis. A meta-analysis performed by Aiolfi *et al.*^[9] showed no differences in term of postoperative outcomes and complications between laparoscopic and robotic approaches in the short term. A national database review found that robotic repairs showed a lower overall complication rate when compared with open or laparoscopic approaches^[10].

The Robotic Inguinal vs. Transabdominal Laparoscopic Inguinal Hernia Repair (RIVAL) trial demonstrated no added benefit for robotic surgery compared to laparoscopic surgery for unilateral primary or recurrent hernia repairs; however, they have also concluded robotic surgery plays a role in specific settings^[11]. Furthermore, due to technical difficulties, complex inguinal hernia repairs (scrotal hernias, incarcerated hernias, recurrent hernias, mesh removal, and previous pelvic surgery) are a relative contraindication for laparoscopic repairs^[6]. In this article, we highlight the advantages of the robotic approach for complex cases of inguinal hernia.

The road map for safety in MIS hernia repair

The evolution of MIS inguinal hernia repair has mirrored the evolution of laparoscopic cholecystectomy. Surgeons have developed an analogous idea of safety for MIS inguinal hernia repair^[4,12-14]. This concept has created a road map to maintain a safe and efficient laparoscopic approach for inguinal hernia repair. As more and more surgeons perform MIS repair for inguinal hernias, this road map is conceptualized to provide a standard dissection and posterior repair.

Furthermore, the posterior anatomical view of the groin might be challenging even for experienced surgeons. Furtado *et al.*^[15] has developed a concept to understand the groin's posterior anatomy by identifying anatomical landmarks and important triangular areas to avoid injury of noble structures. The combination of the stepwise critical view of safety with the identification of anatomical landmarks has created a safe alternative for surgeons worldwide to perform an effective MIS inguinal hernia repair. Claus *et al.*^[4] have condensed this road map in the 10 golden rules for a safe MIS inguinal hernia repair that can be easily adapted for the robotic approach [Table 1].

Robotic inguinal hernia repair after prostatectomy

The most common complications after radical prostatectomy are impotence and urinary incontinence^[16]. Inguinal hernia is another common complication confirmed by several studies^[17-20]. A meta-analysis published by Alder *et al.*^[16] has shown a high incidence of inguinal hernia after open radical prostatectomy followed by laparoscopic and robotic prostatectomies. There was no difference between both MIS repairs^[16].

Different studies have been published showing the feasibility of performing rIHR concomitant to radical prostatectomies^[21,22]. Clinically, non-diagnosed inguinal hernias before the surgical procedure are found in 20% to 33% of robotic prostatectomies^[23]. There is a lack of data regarding the recommended approach for inguinal hernia repair after prostatectomies. Furthermore, the HerniaSurge guidelines recommended surgeons to consider an anterior approach when performing hernia repair in patients with prior urologic

Table 1. Ten steps for a safe MIS inguinal repair

Step 1: Pre-peritoneal access: high flap on TAPP vs direct access in TEP
Step 2: Peritoneal plane to protect retroperitoneal nerves
Step 3: Medial dissection should reach the midline and dive into Retzius
Step 4: Femoral hernia needs to be excluded by visualization of femoral orifice
Step 5: Posterior dissection of peritoneum until psoas muscles and iliac vessels to parietalize the elements of the cord
Step 6: Large and long indirect sacs may be transected to minimize trauma to elements of the cord
Step 7: Active exploration of the deep inguinal ring should be done to exclude and/or reduce cord lipomas
Step 8: Minimal 3-4 cm overlap of all defects should be granted with a mesh with the minimum size of 15 cm × 10 cm
Step 9: Most of cases do not need traumatic fixation
Step 10: Final step of preperitoneal deflation on TEP or peritoneal closure on TAPP should ensure no mesh displacement

MIS: Minimally invasive surgery; TEP: totally extraperitoneal repair; TAPP: transabdominal preperitoneal repair.

pelvic operations in their 2018 guidelines^[5]. The scar tissue formed after the pelvic operation may turn the inguinal repair more challenging with further complications. The scarred tissue planes can limit the ability to do a proper medial dissection and lead to a bladder injury or a major vascular injury over the iliac vessels after lymph node dissection is performed during the radical prostatectomy. The robotic approach may bring some advantages to otherwise a more challenging repair by MIS technique. Surgeons working with instruments with improved dexterity and a high-definition 3D vision may allow performing a successful procedure with low complication rates.

Despite the HerniaSurge guidelines, many studies have been published showing the laparoscopic approach for inguinal hernias after prostatectomies^[24-28]. There are two studies in the literature regarding robotic inguinal hernia repair after urologic procedures to our knowledge. Angus *et al.*^[29], using the Americas Hernia Society Quality Collaborative (AHSQC) database developed by the Americas Hernia Society, identified 65 male patients submitted to rIHR after a prostatectomy. Performing a propensity match score with 3:1 patients submitted to a robotic repair, the group with previous urologic surgery had no difference compared to the control group in intra-operative and post-operative complications, 30-day recurrence, and re-admissions of surgical site outcomes. As this is certainly an encouraging result with a limitation of the retrospective design of the study. Dewulf *et al.*^[30] published their experience with a cohort of 22 patients submitted to robotic inguinal repair after prostatectomy. There were no intraoperative complications, no conversions to open or laparoscopic surgery and at 4 weeks of follow-up, 22.7% had an asymptomatic seroma^[30]. Also, more studies and trials are needed to demonstrate the robotic approach's safety and feasibility in these challenging cases.

Surgeons may be navigating in unknown waters during these procedures. Fibrosis from the previous lymph node dissection may alter the anatomy on top of the external iliac vessels, and extra attention is necessary for avoiding a major vascular injury. The bladder dissection is more difficult and the filling of it with saline may help to identify the proper plane. Any injury should be recognized and promptly repaired. A leak test may be performed with dye after the dissection to rule out any missed bladder injury. The enhanced 3D vision of the robotic platform with a scaling of movements, associated with the increased dexterity of the surgical instruments with tremor filtering, may be beneficial in identifying structures and avoiding those major injuries.

In our academic center, the tips and tricks described above were essential to performing a safe robotic inguinal repair in 11 patients who were previously submitted to a prostatectomy, without major intraoperative or postoperative complications.

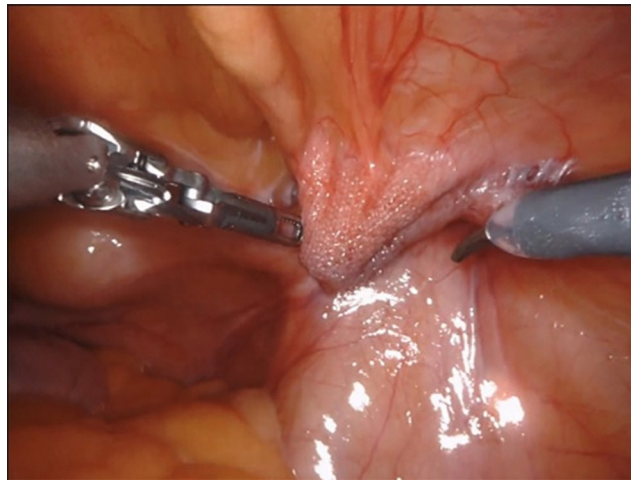


Figure 1. Identification of right-side inguinal plug before robotic mesh explantation.

Robotic mesh explantation

Most hernia repairs in the United States are performed with mesh^[31]. As more meshes are implanted, more may need to be removed due to complications^[32].

Mesh infection, mesh-related pain, meshoma, recurrence, chronic pain, and entrapment of the nerve are reported as the main indications for mesh removal^[33-35].

Studies have shown that chronic pain rates after MIS inguinal repair are lower than those after open inguinal repairs^[36,37]. The main advantage of endoscopic repair on reducing chronic pain is avoiding nerve dissection for mesh implantation and avoiding traumatic fixation.

There are different options to manage patients with chronic pain after inguinal hernia repair. In certain situations, removing the mesh (mostly plugs) is necessary for addressing the problem [Figure 1]. Open mesh removal is an established technique, but scarred tissue from the previous repair may alter the anatomy, and injury to the critical structures may happen. Laparoscopic mesh removal may be incredibly challenging due to the innate nature of straight instruments and 2-dimensional vision.

One possibility is to use the robotic platform. Truong *et al.*^[35] have described a step-by-step guide for removing the pre-peritoneal mesh using the robotic platform. The robotic mesh explantation (RoME) is feasible due to the same advantages as discussed for inguinal repairs after prostatectomies. It may be less challenging to work on the scarred tissue using robotic articulated instruments than using classic laparoscopic instruments.

Two concepts are essential for operating in the inflamed and fibrotic areas. The first one is starting the dissection over virgin planes facilitates access to the area where the mesh is scarred to vital structures. The second one is to dissect on and at the mesh while trying to free the mesh from the surrounding adhered structures. The aim of mesh explantation is to decrease the burden of foreign body material as much as possible without compromising vital structures. It is considered an acceptable practice to leave a small piece of the foreign body material behind. A negative margin is not necessary as in oncologic procedures. In inguinal mesh removal, the nerves are usually involved, and neurectomies are often necessary.

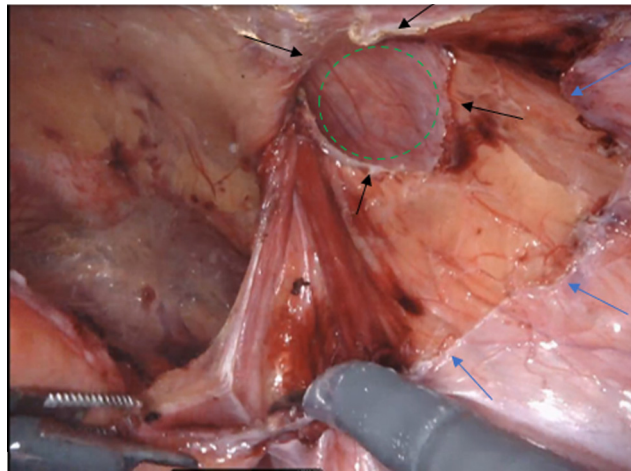


Figure 2. Right side inguinoscrotal hernia. Green circle shows large indirect inguinal hernia defect. Black arrows show distal edge of the indirect hernia sac after transection and blue arrows show proximal edge of the transected sac.

Our initial experience of 10 inguinal RoME proved to be safe with no major complications, once executed by an experienced surgeon.

A preoperative pain mapping is crucial for evaluating these patients to determine which nerves are affected. The genitofemoral and lateral-cutaneous nerves are the most common nerves involved during MIS inguinal hernia repair. Furthermore, orchiectomy may be necessary, and all these complications should be discussed with the patients and addressed in the consent. The robotic platform may be the best option to navigate through these challenging situations with minimal damage.

Robotic inguinal repair in inguinoscrotal hernias

Inguinoscrotal hernias represent a challenge for minimally invasive surgeons, and its management is still debatable^[38]. Early reports on laparoscopic TAPP repair of inguinoscrotal hernias and guidelines of endoscopic repair of scrotal hernias validated the MIS approach^[39,40]. However, there is no consensus on the best surgical approach.

Despite many reports in the literature regarding robotic TAPP for inguinal hernia repairs, there is a paucity of studies regarding inguinoscrotal hernias^[41]. Yheulon *et al.*^[41] demonstrated rIHR in 14 patients with inguinoscrotal hernias with no major complications. Seroma was the most common complication. These cases may be more challenging using regular laparoscopic instruments and the robotic platform, with the articulated instruments, enhanced visualization and the ability to control a fourth arm, may allow the surgeon to perform these complex cases with few post-operative complications.

Morrell *et al.*^[38] demonstrated a laparoscopic technique showing a special technique for those complex inguinoscrotal hernias. The primary abandon-the-sac technique performed in 26 patients was based on an incomplete dissection of the distal sac, leaving it into the inguinal canal and scrotum [Figure 2]. This technique can be safely used in patients with inguinoscrotal hernias. Seroma seems to be its main complication, but it avoids hematomas and possible ischemic orchitis from extensive dissection of the cord structures. Siow *et al.*^[42] demonstrated a modified laparoscopic TAPP technique for incarcerated scrotal hernias with a scrotal incision in 20 patients. This modification has facilitated performing an MIS repair for large and complex inguinoscrotal hernias, which would otherwise be managed by an open technique.

CONCLUSION

Management of complex inguinal hernias is challenging. Adequate surgical knowledge and mastery of inguinal anatomy are essential for the surgical technique's success. The robotic platform would enable us to perform otherwise a technically challenging MIS procedure safely. Robotic surgery is still in the early phase of adoption for inguinal hernia repairs. More well-designed studies are needed to evaluate its efficacy in groin hernia repairs.

DECLARATIONS

Authors' contributions

Manuscript preparation and editing: Lima DL, Lima RNCL, Sreeramoju P, Malcher F
Study design: Malcher F, Lima RNCL, Lima DL, Sreeramoju P

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Dr. Lima DL, Lima RNCL, Sreeramoju P disclose no financial relationships with industry or conflicts of interest.

Dr. Malcher F discloses consulting fees from BD & Medtronic, outside the submitted work.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Technical Note

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Deep learning-driven catheter tracking from bi-plane X-ray fluoroscopy of 3D printed heart phantoms

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Abstract

Minimally invasive surgery (MIS) has changed not only the performance of specific operations but also the more effective strategic approach to all surgeries. Expansion of MIS to more complex surgeries demands further development of new technologies, including robotic surgical systems, navigation, guidance, visualizations, dexterity enhancement, and 3D printing technology. In the cardiovascular domain, 3D printed modeling can play a crucial role in providing improved visualization of the anatomical details and guide precision operations as well as functional evaluation of various congenital and congestive heart conditions. In this work, we propose a novel deep learning-driven tracking method for providing quantitative 3D tracking of mock cardiac interventions on custom-designed 3D printed heart phantoms. In this study, the position of the tip of a catheter is tracked from bi-plane fluoroscopic images. The continuous positioning of the catheter relative to the 3D printed model was co-registered in a single coordinate system using external fiducial markers embedded into the model. Our proposed method has the potential to provide quantitative analysis for training exercises of percutaneous procedures guided by bi-plane fluoroscopy.



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Keywords: Catheter tracking, image guidance, deep learning, 3D printing, minimally invasive surgery, 3D trajectory, percutaneous interventions, patient-specific

INTRODUCTION

Since minimally invasive surgery (MIS) emerged in the 1980s, surgical skills and minimally invasive equipment have achieved significant advancements^[1-3]. The minimally invasive approach holds a unique place for various surgical specialties, such as general surgery, urology^[4], thoracic surgery^[5], plastic surgery^[6], and cardiac surgery^[7]. MIS has not only improved the recovery time of patient's from specific procedures, but is also enabled to provide improved outcomes^[8,9]. These benefits to patients, hospitals and physicians have attributed to the rapid development of new MIS procedures, including cardiovascular diseases. The success of cardiac interventions over the last three decades has significantly reduce the mortality and morbidity of coronary, valvular, and various congenital diseases^[10,11]. However, expansion of MIS to more complex surgeries demand further development of new technologies, including robotic surgical systems^[12], navigation^[13], guidance^[14], and visualizations^[15], dexterity enhancement^[16], and 3D printing technology^[17].

In recent years, 3D printing technology has been attractive in diverse areas of medicine, including cardiovascular disease^[18]. Increasing interest in anatomical modeling and the growing need for pre-operative planning using personalized anatomical models to test for device fit and practicing catheter positioning have encouraged the creation and evolution of 3D printed patient-specific models^[19]. Recently, there are several studies showing various implementations of 3D printed heart models for different stages of structural heart interventions, such as pre-operative planning^[20-23], intra-operative models for enhanced structural orientation^[24-26], and evaluations of novel procedural pathways^[27,28]. Garekar *et al.*^[29] utilized a 3D printed model for a double outlet right ventricle. The study showed the 3D printed model provided better intuition to decide on an operative approach than conventional imaging (i.e., echocardiography)^[29]. Chaowu *et al.*^[23] demonstrated a 3D printed model for transcatheter closure of secundum atrial septal defect, where their findings suggested that 3D printing has the potential to screen for appropriate candidates. Other examples include tetralogy of Fallot^[22,30], hypoplastic left heart syndrome^[31,32], and ventricular septal defect^[33,34]. Despite the successful implementation from prior work, the existing surgical planning from 3D printed models does not have methods to analyze how a catheter had actually maneuvered in the 3D printed model.

Our group recently reported a novel training system that provides catheter navigation in mixed reality (MR), with real-time visual feedback of a physical catheter's position within a patient-specific 3D heart model^[35]. This method used electromagnetic (EM) sensors to track the catheter position. Although this method is advantageous for portability, it has a low accuracy (up to ~5 mm), requires manual integration of sensors into a catheter, and the hardware not readily available in catheterization labs.

To address these limitations, we propose a novel deep learning-driven method for tracking a catheter in a 3D printed model from bi-plane fluoroscopic images acquired during the procedure. The catheter and heart position are co-registered in a single coordinate system using affine transformations based on four fiducial radiopaque markers, which are located on the 3D printed model. Additionally, the 3D trajectory of the catheter is produced, visualizing the path taken during the mock procedures. Our proposed method has the potential to provide quantitative analysis for training exercises of percutaneous procedures guided by bi-plane fluoroscopy.

Methodology

A schematic of the proposed training system is shown in [Figure 1](#), where a physician conducts a mock catheterization procedure using a bi-plane C-arm X-ray fluoroscopy machine on a patient-specific 3D printed model. The proposed image tracking aims to detect and co-register the catheter's 3D position and provide a 3D trajectory as quantitative feedback. Different features that are utilized for our proposed tracking system are described in detail in the following subsections, which are in the order by which this process is conducted.

3D printed phantom model

To 3D print a patient-specific model, we used a 3D image processing software (Materialize Mimics Research software 21.0) to import an end-diastolic cardiac computed tomography (CT) scan as a DICOM (Digital Imaging Communication in Medicine) data file, shown in [Figure 2A](#). In Mimics, the specific thresholds are set to segment the heart and the spine, enabling a 3D representation of the heart and spine in one mask while maintaining all the relative positions. Then, the 3D segmentation is saved as a STL file. To trim all the vessels, ribs, and other elements that are not necessary for the model, we used Geomagic Wrap (3D Systems Geomagic Corporation, NC, USA). Additionally, as depicted in [Figure 2B](#) and [C](#), the artifacts were removed, and the meshwork was smoothed. Finally, using the “Shell” tool in Geomagic, the model obtained a water-tight thickness, and cleaned reconstructed objects were saved as STL files. Moreover, we utilized Solidworks software 2018 (Dassault Systems) to incorporate the supporting base structure for the heart and spine, fixing their relative distance during printing and use [[Figure 2D](#) and [E](#)]. This study used Stratasys Object Connex 260 printing system and the rigid and translucent material named VeroClear [[Figure 2F](#)]. Additionally, the post-printing process (i.e., removing supporting SUP705 Stratasys material) was conducted using a high-flow water jet cleaner (i.e., Powerblast) and art supply sculpting tools. In order to conduct mock catheterization procedures under a C-arm X-ray fluoroscopy machine, we integrated the phantom model into a 5-sided acrylic box (shoppopdisplays.com). The model is then glued in the center of the box with its inlet- and outlet-facing holes that were drilled at two opposite ends of the box [[Figure 2G](#)]. Throughout the fluoroscopic imaging, the box is filled with water, eliminating artifacts from the 3D printed model.

Deep learning architecture

The advancement of deep learning architectures like convolutional neural networks (CNN) and deep autoencoders not only transformed typical computer vision tasks like object detection^[36], but are also efficient in other related tasks like classification^[37], localization^[38], tracking^[39], and image segmentation^[40,41]. Ronneberger *et al.*^[41] proposed the state-of-the-art U-Net by replacing the pooling operators in Fully Convolutional Network^[42] with upsampling operators, allowing the input image's resolution retention. U-Net's performance in segmenting medical images, notably with a small training dataset, promises the potential of such Encoder-Decoder architecture. The U-Net model was later extended for processing other medical images, including, but not limited to, the Xenopus kidney^[43] and MRI volume segmentation of prostate^[44], retinal vessels, liver and tumors in CT scans, ischemic stroke lesion, intervertebral disc and pancreas^[45-52]. In this work, to track the catheter's position from the bi-plane fluoroscopic images, we primarily leveraged the U-Net model to detect a radiopaque marker at the tip of the catheter. The details of implementation and framework will be discussed in the following sections.

Collection and preparation of datasets

All fluoroscopic images for training the deep learning U-Net model were acquired during the mock procedures in the catheterization lab at New York-Presbyterian Hospital. The datasets comprise 300 paired bi-plane images pertaining to the maneuvering of a catheter (OSCAR Deflectable Steerable Guiding Sheath, Destino™ Twist) within the patient-specific 3D printed model. The datasets were divided into 3 parts: (1)



Figure 1. Schematic of the proposed training system. (A) Image of 3D printed heart model on a bi-plane c-arm. (B) Magnified view of patient-specific 3D printed heart model. (C) Schematic of image transfer process and post-processed catheter tracking. (D) Image-processing and deep learning steps of bi-plane images with tracking plot.

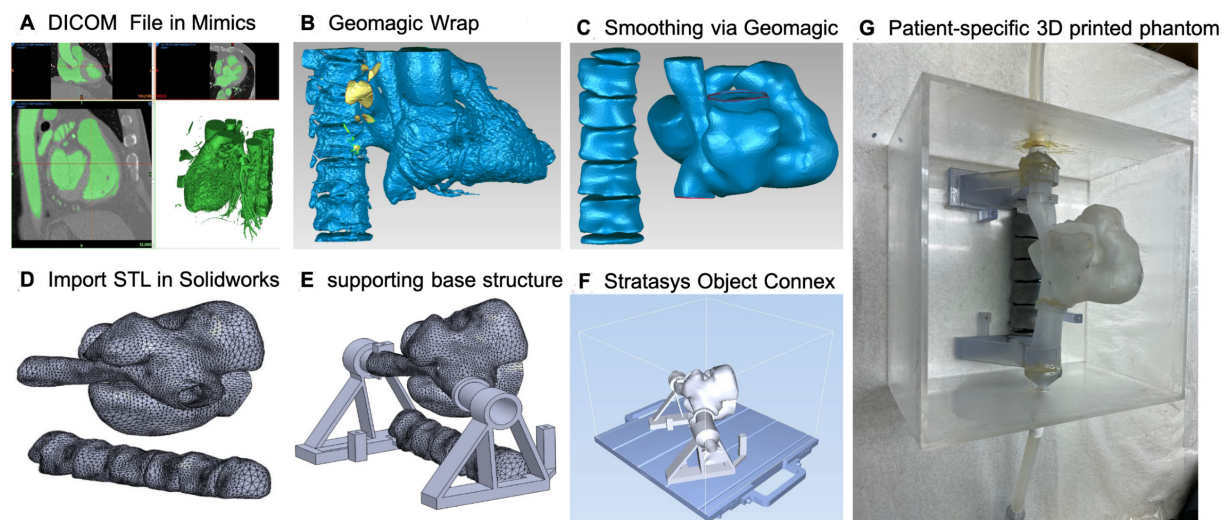


Figure 2. Depicting workflows of patient-specific 3D printed model. (A) Segmentation of heart and spine from DICOM file. (B, C) Import CAD into Geomagic Wrap for post-processing. (D, E) Import CAD into Solidworks to add support structures. (F, G) 3D print CAD, spray spine with metallized spray for opacity, and integrate both into acrylic box.

training set (60%; 180 images); (2) validation set (20%; 60 images); and (3) testing set (20%; 60 images). The training and validation set were used during model training. The testing set was used for model evaluation at the end of the model training. To ensure that both our training and test dataset contain a fair representation of the catheter's tip and avoid overfitting, we randomly shuffled datasets before splitting them into training and test sets.

Training

The overall steps in our developments of a deep learning model are as follows: (1) randomly initialize the model; (2) train the model on the training set; (3) evaluate the trained model's performance on the validation set; (4) choose the model's hyperparameter with the best validation set performance; and (5) evaluate this chosen model on the test set. An adaptive moment (ADAM) estimation was used for training the CNNs^[53]. The loss function was set to the binary cross-entropy. An early stopping rule was applied with 200 epochs. Finally, we evaluated the performance of the DL model by computing accuracy metrics and determined the Dice coefficient on the testing set.

Co-registration algorithms

A key step in this system is to co-register the catheter and heart model in a single coordinate system. To this end, four metal spheres were embedded in our heart phantom model and used as fiducial markers. As shown in Figure 3A, the catheter and all four fiducial markers are visible in both of the bi-plane fluoroscopic images, such that they will be tracked and processed using the OpenCV library in Python. The OpenCV processing comprises Bitwise-Not operation, Smoothing operation, and Contours operation, illustrated in Figure 3B and C. Next, the radiopaque markers' 2D coordinates are identified from both fluoroscopic images (RAO30°, LAO55°) and fed into the co-registration algorithms. Utilizing one of the radiopaque markers as a reference, the other coordinates will be offset. With the offset position of the fiducial marker and the known rotation angle, the 3D positions are solved from equation 3, as shown in Figure 3D. Then, the positions of four predefined fiduciary markers are used to calculate the affine transformation matrix in a single coordinate system using Eq. 4 and Eq. 5. The positions of four fiduciary markers are used to calculate the affine transformation matrix in a single coordinate system. Finally, the transformation matrix is applied to the position of the catheter's tip, as retrieved from a U-Net model prediction, to be co-registered in the coordinate system.

RESULT AND DISCUSSION

Bi-plane co-registration accuracy

To validate the accuracy of our 3D co-registration algorithm, we 3D printed a jig that holds an array of 50 metal spheres at various heights, shown in Figure 4. Using the biplane C-arm, two fluoroscopic images from two different angles were acquired and processed as described in section 2.5. Finally, the absolute error for each sphere was determined based on the difference between the true value measured from the 3D CAD file and the calculated value from the processed bi-plane images using our co-registration algorithm. As can be seen from Figure 4C, the average accuracy was 0.12 ± 0.11 mm, which is highly accurate for cardiac interventions.

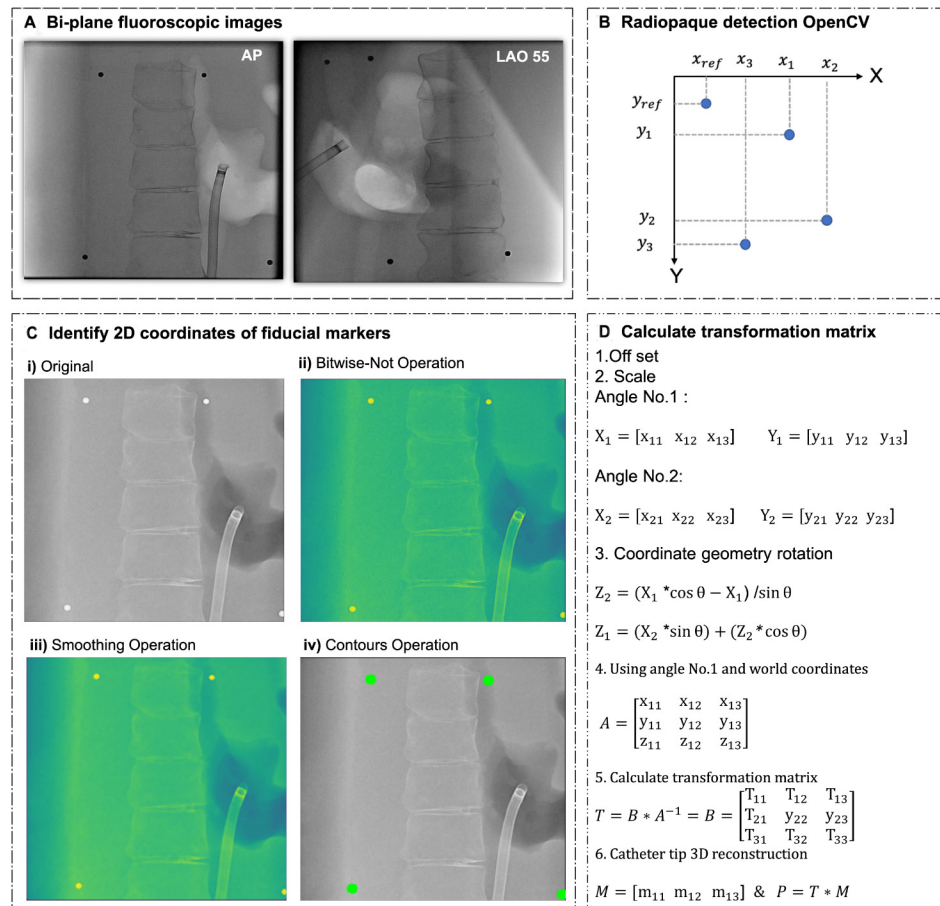
Catheter tip detection

The primary region of interest of a catheter during a procedure is its tip. Any intra-operative errors due to catheter tip maneuvering in the vascular system may raise the risk of puncture, embolization, or tissue damage^[54,55]. As a result, we trained a deep learning U-Net model to detect the catheter tip's radiopaque marker in each frame of the fluoroscopic images. Figure 5 depicts the groundtruth and predicted segmentation of the catheter tip's radiopaque marker for the testing dataset. To evaluate the model performance, we used the area-based indexes to compare the predicted segmentation results with the groundtruth. These indexes include the Dice coefficient (DSC)^[56], Binary cross-entropy, and Intersection over Union (IOU) which can be found in Table 1. In order to improve the performance of the U-net model over our datasets and avoid the overfitting training phase, we performed extensive data augmentation^[54], including random shifting, scaling, rotation, and brightness/contrast changes, shown in Figure 6. Throughout each augmentation experiment, the IOU for each image and the mean average for the entire testing datasets (60 images) were calculated. We found that the best performance occurred by applying 10 random translations per image (± 20 pixels), scaling with a zoom range of 0.1, 10 regular rotations per image, and random brightness and contrast of 0.5 resulting in 83.67% IOU. It should be noted that our reliable segmentation score (Dice of 0.8457 and IOU of 0.8367) resulted in an accuracy of (< 1 mm), which is far beyond the acceptable range for catheter tip tracking in cardiac applications.

To highlight the deep learning segmentation task's accuracy and efficiency, we compared the performance of the U-Net architecture with some classical image processing techniques (i.e., Thresholding, Watershed, Find and draw Contours by OpenCV, etc.). The catheter's radiopaque marker's appearance is affected by partial occlusions, intensity saturation, and motion blur. As can be seen from Figure 5, and despite the

Table 1. Dice, Precision, and Recall metrics evaluation of catheter tip's radiopaque marker testing set for segmentation task by U-Net model

Method	Catheter tip's radiopaque marker segmentation		
Indexes	Dice coefficient	Binary cross-entropy	Intersection over Union
Deep learning U-Net model	0.8457	0.3512	0.8367

**Figure 3.** Illustration of sequential steps to co-register bi-plane fluoroscopic images (AP, LAO 55) utilizing four fiduciary radiopaque markers. (A) Raw fluoroscopic bi-plane images. (B) Radiopaque marker detection using OpenCV library. (C) Identify 2D coordinates of fiducial markers. (D) Co-registration algorithms to calculate the affine transformation matrix to combine all points into a single coordinate system.

widespread use of such methods (i.e., adaptive thresholding), they are prone to systemic noise and unreliable measurements, mainly due to the assumptions made in the computational design algorithms and failing to identify separable boundaries.

Trajectory of catheter movement

Fluoroscopy only provides a 2D projection image, and therefore no depth information is visible in the image^[57]. Alternatively, fusion imaging allows for 3D imaging data of the heart tissue to be overlaid on a fluoroscopic image; but this technology has the drawback that the catheter and rendered tissue is only seen as a 2D projection, providing little to no post-procedural quantitative analysis. To this end, we demonstrate the 3D trajectory of the catheter derived from bi-plane co-registration method. The 3D trajectory of a

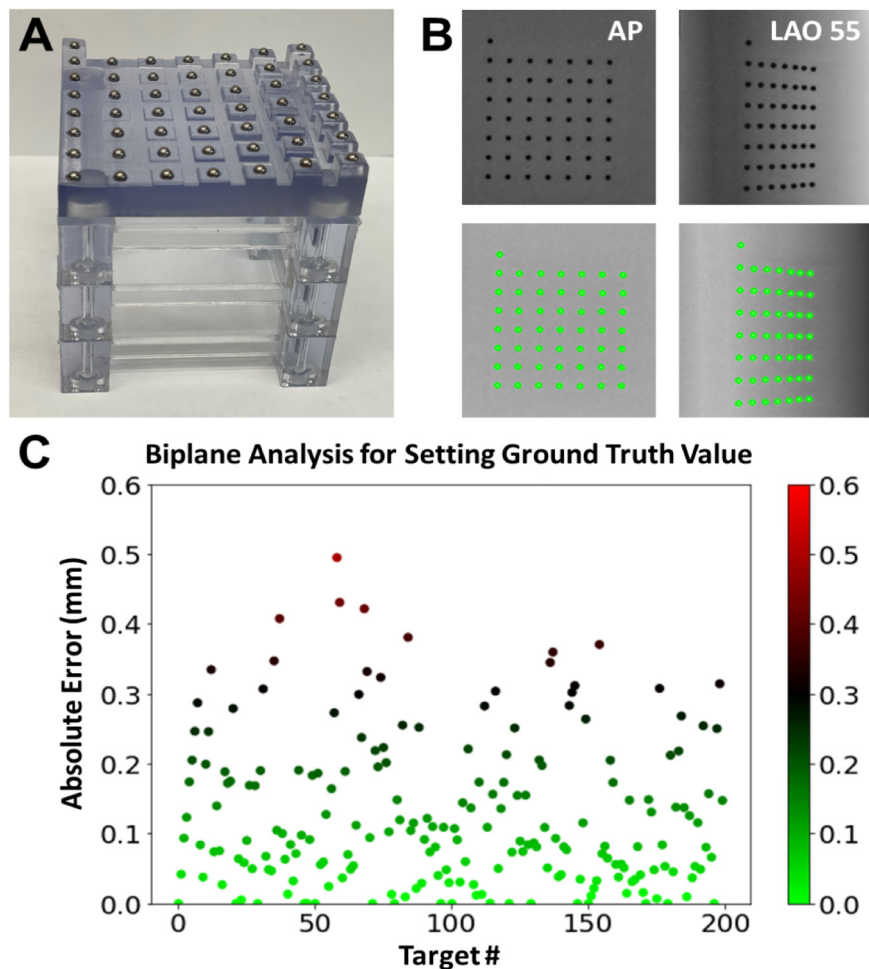


Figure 4. Validating 3D co-registration algorithm. (A) Image of 3D printed jig holding array of 50 metal spheres at various heights. (B) Image of fluoroscopy images at two angles and auto-detection of those spheres. (C) Graph of error for each sphere based on true value measured from 3D CAD file for bi-plane.

catheter is vital information for determining how a procedure was performed and providing a quantitative basis for analysis and future improvements. Figure 7A shows the selected fluoroscopic frames (LAO56°, RAO30°) acquired at the beginning and end of a mock procedure in the 3D printed model. After the catheter tip was detected from the two fluoroscopic images (i.e., RAO30°, LAO56°), the tip's coordinate (from LAO56°) and the derived transformation matrix (from Eq. 5) was used to co-register the catheter in a single coordinate system as described earlier in section 2.5. Figure 7B shows the catheter tip's 3D trajectory for the mock test.

CONCLUSION

This work demonstrates the implementation of a deep learning U-Net architecture to track the 3D movement of a catheter during a mock cardiac intervention under bi-plane fluoroscopy. We leveraged an end-diastolic cardiac CT in order to 3D print a patient-specific phantom model. We integrated four fiducial radiopaque markers on the phantom model, allowing us to co-register fluoroscopic images taken at two different angles (RAO30, LAO55). The U-Net model was trained in a supervised manner on the training set, and the trained model's performance was evaluated on the validation set. Finally, we assessed the DL model's performance by computing accuracy metrics and determining the Dice coefficient on the testing

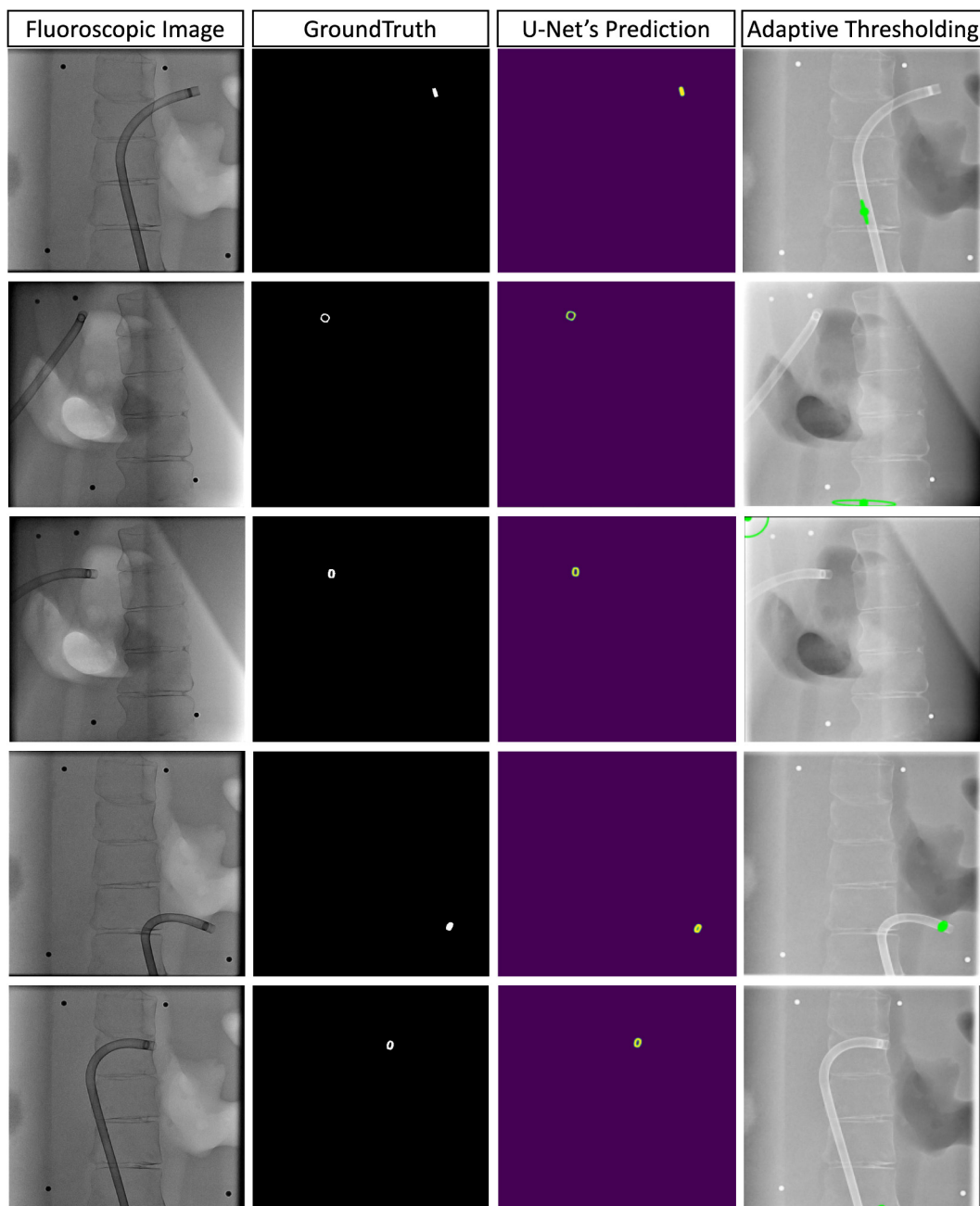


Figure 5. Comparison of catheter tip detection using the U-Net model and adaptive thresholding. Illustration of raw fluoroscopic images, groundtruth, and predicted segmentation for the two testing datasets.

set. Additionally, we demonstrated the 3D trajectory of the catheter tip's movement can be visualized graphically.

We believe the 3D trajectory analysis performed by this model can be used to analyze a physicians' performance and/or provide quantitative feedback for training and educational purposes. This work serves as a proof-of-principle that deep learning can be used for catheter tracking for cardiac interventions, however, since this article is a technical note, it has several limitations in its current stage, and we believe these limitations will be the seed for future developments for both our lab others. These limitations include:

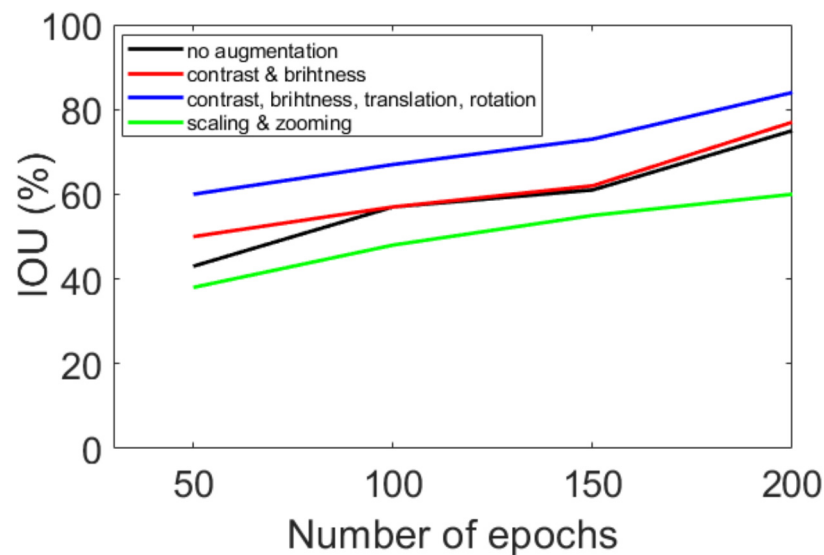


Figure 6. Relationship between the number of epochs for training, the data augmentation, and Intersection over Union (IOU). The applied augmentation including 10 regular rotations per image, 10 random translations per image (± 20 pixels), brightness = 0.5, contrast = 0.5, scaling = 0.1. The IOU percent is the mean average of IOU over 60 testing datasets.

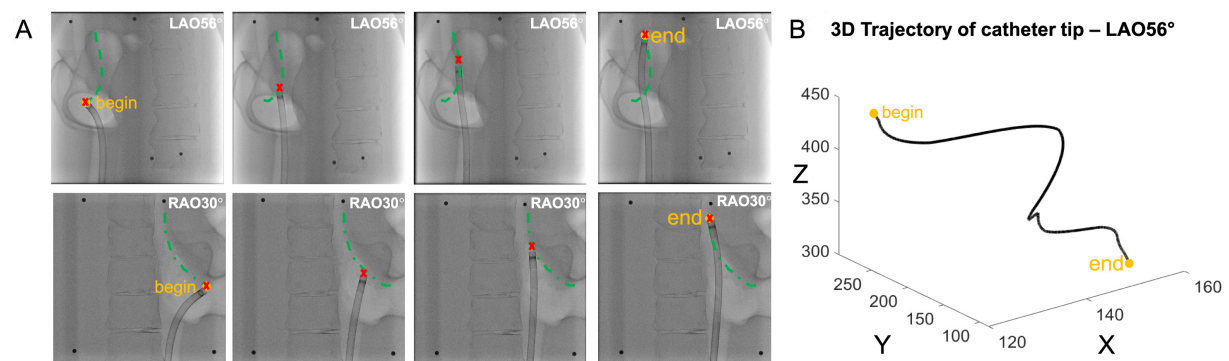


Figure 7. (A) Illustration of selected fluoroscopic frames (LAO56° and RAO30°) enclosing the beginning of mock procedures to the end. (B) LAO56° 3D trajectory of catheter tip retrieved from bi-plane co-registration.

(1) Limited data sets. Currently our dataset is only trained on a single 3D printed heart model and catheter. Therefore, a much more expansive dataset is needed to train a model that can accurately track catheters of different shapes and sizes and in hearts of differing anatomy. (2) Unrealistic background. Although these 3D printed models are patients-specific, meaning they accurately recapitulate the anatomy of the heart and spine, the fluoroscopic images don't include image artifacts from other surrounding anatomy, as will be the case for clinical images. (3) Limited analysis. Currently our model is only able to provide a 3D tracking of the catheter's tip, but there is no subsequent analysis to provide metrics for the performance of the intervention. This will require understanding the goals of the procedure and defining key metrics that can be quantified and will be useful for the physician. (4) No motion-compensation. The position of a catheter relative to the human heart is time-varying due to both respiration and cardiac contractions. Since we're using a 3D printed model there was no motion to compensate for, however, solutions will need to be integrated for the catheter tracking to properly co-register the catheter tip to the heart in a clinical procedure. (5) Spherical fiducial markers. Since a 3D printed model was used, it was convenient to use metal spheres as extrinsic fiducial markers. However, placement of these spheres on an individual will not

be trivial and therefore methods that utilize the spine as an intrinsic fiducial maker should be used during acquisition of clinical images, as described in our previous work^[58].

Due to the above listed limitations, this work will have the most immediate impact for performing quantitative analysis of training procedure on 3D printed heart models. We expect that more sophisticated heart models that include motion and match disease states will be created, along with specific criteria for success for each model/intervention to provide feedback in the form of quantitative metrics. Furthermore, the ability to process images in real-time and display the catheter in MR renderings will improve training by providing assistance during the training session, as described in our previous work that adopted EM sensors for tracking^[35]. We believe this tracking system will serve to lower the learning curve for new fellows and refine the procedural techniques of attendings.

DECLARATIONS

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Authors' contributions

Conceived of the presented work: Mosadegh B, Torabinia M

Took the lead in writing the manuscript: Torabinia M, with support from Mosadegh B

Carried out the experiment: Caprio A, Torabinia M

Involved in processing and analyzing the datasets: Jang S, Ma T, Tran H, Mekki L, Chen I, led by Torabinia M

Supervised the theoretical and deep learning framework: Sabuncu M, Mosadegh B

Supervised the image acquisition: Wong S, Mosadegh B

All authors discussed the results and commented on the manuscript.

Availability of data and materials

Not applicable.

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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Diagnosis and treatment of biliary malignancies: biopsy, cytology, cholangioscopy and stenting

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Abstract

Biliary tract malignancies include cancers of the intra-hepatic and extra-hepatic bile ducts. Cholangiocarcinoma is the predominant biliary tract malignancy with nearly 60% of them occurring in the peri-hilar region. They can present with biliary strictures causing jaundice but can be insidious and present late in their clinical course. Recent advances in imaging and other diagnostic modalities help in the earlier identification of these tumors. Diagnosis should be suspected in anyone presenting with jaundice with evidence of biliary ductal dilatation or in patients with primary sclerosing cholangitis with worsening clinical status. The diagnostic approach consists of obtaining tumor markers, mainly CA 19-9, imaging modalities which include computed tomography and/or magnetic resonance imaging to establish the level of biliary obstruction and presence or absence of mass. Tissue sampling is performed with endoscopic retrograde cholangiopancreatography (ERCP) guided cytology and biopsies and with endoscopic ultrasound (EUS) if a mass is visible on imaging. Indeterminate strictures after initial biopsies could be further evaluated by cholangioscopy directed biopsies. Treatment for resectable and distal bile duct cancers involves surgical referral, but palliative biliary drainage is the key for unresectable cancers. Metal stents are generally preferred for distal cancers and plastic stents for proximal cancers. EUS guided biliary drainage can be an alternative approach in patients with failed ERCP.

Keywords: Cholangiocarcinoma, malignant biliary strictures, endoscopic retrograde cholangiopancreatography, stent, endoscopic ultrasound



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INTRODUCTION

Biliary tract malignancies are broadly classified into three categories: (1) intra-hepatic biliary tract cancers; (2) cancer of the extra-hepatic biliary tract and the gall bladder; and (3) ampulla of Vater cancer. Cholangiocarcinoma (CCA) includes tumors of the intra-hepatic bile ducts, peri-hilar and extra-hepatic bile ducts^[1]. Cancers in the distal bile duct can present with biliary strictures due to CCA, pancreatic head cancers or cancer of the ampulla of Vater and they behave clinically similar, thus being broadly categorized as peri-ampullary tumors. Among CCAs, about 5%-10% are intra-hepatic and about 60% of the extra-hepatic CCAs are in the peri-hilar region, classified as the Klatskin tumors^[2] [Table 1]. CCA is the most common biliary tract malignancy but accounts for less than 2% of all cancers^[3]. It is often the most difficult to diagnose among all gastrointestinal cancers with a dismal 5-year survival rate of about 5%^[4]. Risk factors for CCA include primary sclerosing cholangitis (PSC), choledochal cyst, parasitic infections like *Clonorchis*, exposure to thorotrast, hepatolithiasis and familial polyposis but the majority occur sporadically^[5]. Malignant biliary strictures can present with symptoms and signs due to obstruction of the bile ducts including abdominal pain in the right upper quadrant, jaundice, fever or chills due to cholangitis, but they can also be non-specific. They are often insidious in growth and can present late in their clinical course with a poor prognosis. With the advent of advanced imaging technologies, biliary tract malignancies are diagnosed at an earlier stage, offering a potential surgical cure or liver transplant options for patients. Despite all this, only about 20% of malignant biliary obstructions (MBO) are resectable at the time of diagnosis^[6]. This review will address the diagnostic steps for evaluation of MBO due to biliary etiology, tissue sampling methods and the management strategies for biliary drainage, with a predominant focus on CCA.

Diagnostic approach

Diagnosis of a biliary malignancy should be suspected in a patient who presents with symptoms and signs of biliary obstruction, including jaundice, abdominal pain, abnormal liver enzymes with mainly a cholestatic pattern or evidence of biliary ductal dilatation on imaging. Presence of an intra-hepatic mass on imaging warrants further investigation to rule out CCA. In patients with PSC, any deterioration in clinical status with worsening jaundice or weight loss, with or without the presence of biliary ductal dilatation should be further investigated to look for the presence of any dominant stricture and evaluated for CCA, especially in the setting of wall thickening of the bile duct.

The approach for diagnosis depends on the location of the suspected lesion, if it is intra-hepatic, peri-hilar or in the distal biliary tract. Once a biliary tumor is suspected, the patient should undergo further testing with tumor markers, imaging studies and endoscopic or percutaneous procedures for sampling to establish a diagnosis. A tissue diagnosis is generally necessary prior to any surgical planning, documentation prior to non-operative treatment modalities like chemoradiation and especially in indeterminate strictures, where establishing a diagnosis will change the management. Distal biliary tumors can cause both intra- and extra-hepatic biliary ductal dilatation while peri-hilar tumors cause intrahepatic ductal dilatation with normal extrahepatic ducts.

CROSS-SECTIONAL IMAGING STUDIES

Ultrasonography

Trans-abdominal ultrasonography (US) is often the first imaging modality obtained for any patient with abnormal liver enzymes with jaundice or right upper quadrant abdominal pain. US can provide information on biliary ductal dilatation with a possible level of obstruction, presence of gall stones or common bile duct (CBD) stones and intra-hepatic CCA as masses with mixed echogenicity. Direct visualization of a mass in the extra-hepatic bile duct is usually unlikely with US. Albu *et al.*^[7] in their series of 124 patients with extra-

Table 1. Classification of cholangiocarcinoma based on location and morphology

Classification of CCA based on anatomical location
1. Intra-hepatic cholangiocarcinoma
2. Extra-hepatic cholangiocarcinoma (up to second order bile ducts)
(a) Peri-hilar CCA
(b) Distal CCA
Bismuth-Corlette classification of peri-hilar CCA
Type 1: Involving common hepatic duct below the confluence of right and left hepatic ducts
Type 2: Involving the confluence of right and left hepatic ducts
Type 3a: Involving the confluence and extending into right hepatic duct
Type 3b: Involving the confluence and extending into left hepatic duct
Type 4: Involving confluence and extending into both right and left hepatic duct/ multifocal
Classification of CCA based on morphological type:
1. Peri-ductal infiltrating (most common)
2. Mass-forming or exophytic
3. Intraductal papillary

CCA: Cholangiocarcinoma

hepatic CCA showed the sensitivity in identifying distal bile duct tumor to be low at 33% while hilar tumors were higher at 86%. Although it is the first test usually performed, further imaging studies are usually required.

Multi-detector computed tomography

Multi-detector computed tomography (MDCT) is the most commonly used modality and can provide information on intra-hepatic tumors, level of biliary obstruction with more detailed information on strictures compared to US, potentially distinguishing benign from malignant strictures. It also provides information on vascular and lymph node involvement and sites of metastasis^[8]. A meta-analysis of 16 studies by Ruys *et al.*^[9] demonstrated an accuracy of 86% for detecting the ductal involvement of the tumor. The sensitivities for evaluation of hepatic artery, portal vein and lymph node involvement were 83%, 89% and 61%, respectively with specificities of 93%, 92% and 88%, respectively^[10].

Magnetic resonance imaging/magnetic resonance cholangio-pancreatogram

Magnetic resonance imaging/magnetic resonance cholangio-pancreatogram (MRI/MRCP) has the advantage of providing a three-dimensional image of the biliary system and vascular structures^[11]. The information on the extent of the tumor/stricture and resectability has been comparable to MDCT and cholangiography. Zhang *et al.*^[10] in their series showed comparable sensitivities for assessment of resectability for MRI and MDCT of 95% and 94% with a specificity of 69% and 71%, respectively. In a study comparing endoscopic retrograde cholangiopancreatography (ERCP) and MRCP for evaluation of malignant peri-hilar tumors, both modalities identified all the obstructions but MRCP was superior in defining the extent of the tumor^[12]. If MRI/MRCP is to be performed, it should be obtained prior to any endoscopic procedures with drainage, since it makes it difficult to evaluate the biliary tree after decompression with stents. MRI/MRCP is useful prior to ERCP for treatment planning.

Positron emission tomography

The role of positron emission tomography (PET) scan is mainly to detect occult distant metastasis which can change the surgical course in about 20%-25% of the patients^[13]. It could also play a role in identifying CCA in the setting of PSC or indeterminate strictures^[14]. It is not routinely used for staging purposes in CCA but can provide insightful information in the select group of patients. Prior studies have shown its utility in highlighting the “hot spots” in such cases, thus potentially aiding in the diagnosis of CCA, although no clear standardized uptake value (SUV) thresholds have been defined for differentiation between benign and malignant lesions.

Tumor markers

Carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) have been studied for the diagnosis of biliary tumors. Although they may be of some diagnostic value, they are not specific for the diagnosis of biliary tumors, especially since they can also be elevated in some benign conditions^[15-17]. The role of CA 19-9 in patients with PSC is particularly helpful and can help with the diagnosis of CCA, especially if there is a sudden increase in the level^[18]. Studies on CA 19-9 have shown wide variations in sensitivity (46%-90%) and specificity (54%-98%)^[19-21]. It can be elevated in benign conditions like cholangitis, biliary obstruction due to other reasons, liver cirrhosis and other malignancies like pancreatic cancer. Kim *et al.*^[17] in their analysis suggested a cut-off value of 37 U/mL with a sensitivity of 78% and specificity of 83% for the diagnosis of pancreatobiliary malignancies but dropped to 74% and 42% respectively in the presence of cholangitis/cholestasis. CA 19-9 assay can be used for surveillance of CCA in patients with PSC. Levy *et al.*^[21] used a cut-off of 129 U/mL and demonstrated a sensitivity of 79% and specificity of 99% for the diagnosis of CCA, but the positive predictive value was lower at 57%. CEA has demonstrated lower sensitivity and specificity compared to CA 19-9 and can be elevated in other malignancies. If levels of either marker are increased, it may be used to monitor response to treatment in the setting of CCA.

TISSUE SAMPLING TECHNIQUES

Endoscopic retrograde cholangiopancreatography

ERCP is still considered the gold standard for biliary imaging with the ability to obtain tissue sampling for diagnosis. Due to recent advances in imaging modalities with CT and MRI/ MRCP, studies have shown comparable diagnostic accuracy with ERCP^[22]. ERCP is useful in the diagnosis of ECCA and peri-hilar CCA. Cholangiograms reveal a stricture in the biliary tract with or without upstream biliary ductal dilatation. Malignant strictures usually appear as long segments with irregularity and asymmetry with shelving [Figure 1]^[23]. Histopathological diagnosis could be obtained with ERCP with one of the three modalities: (1) brush cytology; (2) aspiration of biliary fluid; and (3) biopsy with endobiliary forceps. The sensitivity of these techniques varies when performed individually versus in combination and carries a specificity of almost 100% [Table 2].

Cytology and aspiration

Bile duct brushings are commonly performed to differentiate benign from malignant strictures. Several studies have shown variable sensitivity rates from 23%-86%^[24]. Kurzawinski *et al.*^[25] in the prospective study of 100 patients with biliary strictures reported a 33% sensitivity for detection of CCA. A meta-analysis of more than 1500 patients by Burnett *et al.*^[26] reported a sensitivity of 42%. Frequently cytology is combined with fluorescent *in situ* hybridization (FISH) or mutation profiling (MP) to increase sensitivity. Kushnir *et al.*^[27] demonstrated in their study that sensitivity for cytology alone was 26% but when combined with FISH and MP, it was 44% and 56% respectively. When all 3 modalities were combined it was 66%. Dudley *et al.*^[28] in their study combined next generation sequencing with cytology improving their sensitivity from 67% to 85%.

Sugimoto *et al.*^[29] demonstrated that aspiration of bile in 76 patients with biliary strictures demonstrated a sensitivity of 32% for the diagnosis of biliary cancers but the sensitivity improved to 70% when aspiration was performed after biliary brushings. The sensitivity also improved with the aspiration of a higher amount of fluid, protruding type tumors compared to flat type and for tumor with longer stricture segments. The Presence of a desmoplastic reaction and inflammatory changes can decrease the sensitivity.

Biliary forceps biopsy

Endoluminal biopsy using biliary forceps is technically more challenging compared to brushings and generally requires a sphincterotomy. It can also be difficult to perform in narrow bile ducts and tumors

Table 2. Sensitivity and specificity of various modalities in the diagnosis of malignant biliary strictures

	Sensitivity	Specificity
ERCP with brush cytology	23%-66%	99%-100%
ERCP with biliary fluid aspiration	6%-36%	NA
ERCP with biliary forceps biopsy	45%-81%	99%-100%
Intraductal ultrasound	88%-94%	86%-90%
Endoscopic ultrasound	43%-90%	78%-96%
Spyglass Cholangioscopy	64%-94%	95%-100%

ERCP: Endoscopic retrograde cholangiopancreatography.

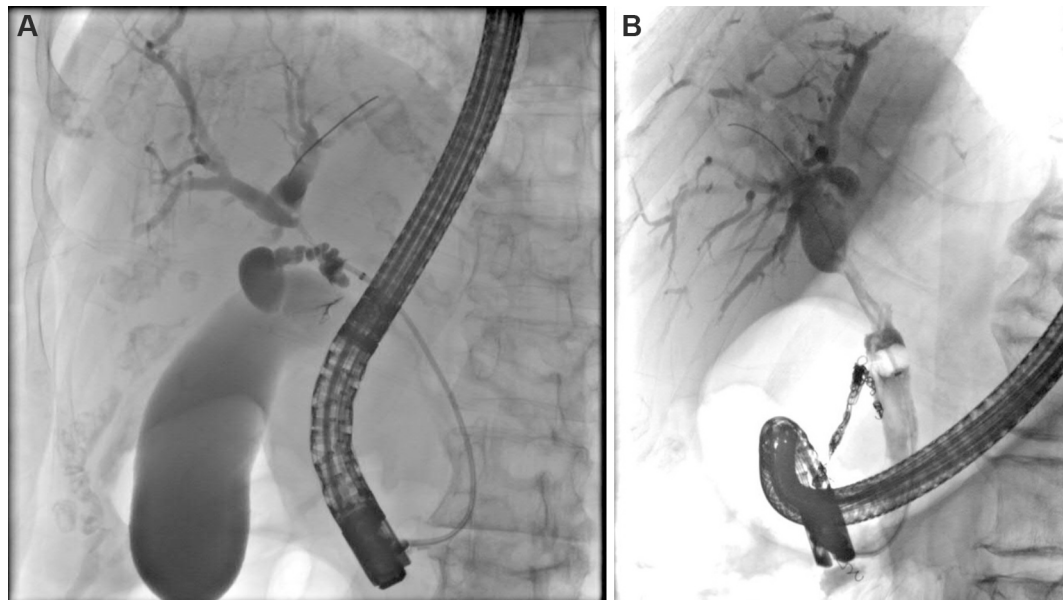


Figure 1. Endoscopic retrograde pancreatography image demonstrating (A) Hilar stricture in a patient with cholangiocarcinoma and (B) Stricture in the common hepatic duct in a patient with cholangiocarcinoma.

higher up in the biliary tree and complications related to tumor bleeding and perforation should be kept in mind. Studies have shown varying sensitivity between 50% and 81% for the diagnosis of biliary cancers^[30,31]. Chen *et al.*^[32] demonstrated a sensitivity of 53.8% for the diagnosis of pancreato-biliary malignancy from biliary strictures, with higher sensitivity for CCA when compared to pancreatic cancer (74% *vs.* 29%). The exact number of biopsies required for diagnosis has been reported to be variable between 1 and 6 in several studies. Tamada *et al.*^[30] showed that infiltrating type biliary malignancies required more bites while 3 biopsies were sufficient to increase the sensitivity to near 100% for papillary type CCA. In order to improve the sensitivity, the combination of brushings along with biliary forceps biopsy has shown better results. A meta-analysis of 9 studies showed the sensitivity for brushings and biopsies to be 45% and 48% respectively but their combination improved it to 59%^[33].

Intraductal ultrasonography

Intraductal ultrasonography (IDUS) consists of high-frequency catheter probes that can be introduced into the CBD over a guidewire most often during ERCP. It is used for the detection of biliary tumors with local staging. There are usually three layers visible on IDUS: an inner hyperechoic layer corresponding to the mucosa, a middle hypoechoic layer of muscle fibers and an outer hyperechoic layer of connective tissue^[34]. The presence of a hypoechoic mass with disruption of normal ultrasonographic pattern and irregular

margins and invasion of the tumor into surrounding tissues are some of the features of malignancy^[35]. Presence of a sessile intra- or extra-ductal tumor and the size of the tumor more than 10 mm were also suggested as high-risk features by Tamada *et al.*^[36]. Studies have also shown IDUS to demonstrate higher sensitivity and specificity when compared to endoscopic ultrasound (EUS) while similar sensitivity and almost similar specificity compared to ERCP guided tissue biopsies, in distinguishing benign and malignant strictures^[37,38]. IDUS can also be useful in guiding biopsies, as the presence of a sessile tumor or high-risk features on IDUS resulted in higher rates of positive sampling. IDUS can also provide information regarding the longitudinal spread of the tumor along the bile duct, depth of tumor invasion and vascular invasion^[39]. Diagnostic accuracy for hepatic artery and portal vein invasion has been reported to be between 86% to 100% in studies^[39]. The drawback of IDUS despite the above advantages is that tissue sampling cannot be obtained, availability mainly in only tertiary care centers and teaching hospitals and requires sufficient expertise to interpret the findings.

Endoscopic ultrasound

EUS can be used in the diagnosis and staging of biliary tract cancers by being able to detect masses that can appear hypoechoic, biliary ductal dilatation and evaluation of the vasculature and lymph nodes for involvement with the tumor^[40] [Figure 2A]. Studies have shown high rates of sensitivity and specificity for detection of malignant strictures up to 80% with detection of distal cancers up to 100% and lower rates for proximal CCAs^[41,42]. Linear EUS scopes provide the ability to perform fine-needle aspiration (FNA), thus improving the diagnostic accuracy [Figure 2B]. With FNA, sensitivity ranging from 43%-90% and specificity ranging from 80%-100% have been reported, with higher rates in distal CCA^[43]. Comparing EUS-FNA with ERCP for diagnosis, studies have shown mixed results with some favoring EUS-FNA and others showing ERCP with biopsies to be superior^[44-46]. But EUS-FNA with ERCP and brushings during the same session has demonstrated superiority compared to EUS-FNA alone^[46]. There are some drawbacks to remember while performing and interpreting the results of EUS-FNA. Studies have shown low negative predictive values ranging from 30% to 65% and hence a negative result does not rule out malignancy in the appropriate clinical setting. An additional complication with EUS-FNA not seen with endo-biliary sampling is tumor seeding after FNA, especially in proximal biliary tumors involving the hilum, as they can lead to peritoneal metastasis. Peritoneal metastasis rates up to 80% have been reported after EUS-FNA sampling^[47,48]. Liver transplantation protocols usually preclude these patients from undergoing transplantation if FNA is performed pre-operatively for hilar malignancies. The concern for tumor seeding is lower with distal biliary strictures and hence EUS-FNA is not a contraindication in such cases.

Despite the use of the above-mentioned techniques, false-negative results are still possible. While a positive result can confirm a diagnosis of malignancy, a negative result does not necessarily rule it out, especially if the pre-test probability is high and these are labelled “indeterminate strictures”. They are defined as strictures with no obvious mass on imaging and cannot be reliably differentiated as benign or malignant, despite workup with ERCP and tissue sampling as described above. Furthermore, the diagnostic yield for strictures due to various etiologies is different, with higher rates for CCA compared to other peri-ductal etiologies like pancreatic cancer and gall bladder cancer, thus adding more confusion in clearly defining these strictures. Surgical exploration can be considered in such cases but recently the use of direct cholangioscopy guided biopsy has led to a reduction in the need for surgeries and provide the ability for direct visualization of these strictures. Despite all the workup, if the concern for malignancy remains high, such patients can be referred to surgery for further exploration.

Cholangioscopy

Digital single operator cholangioscope (DSOC, SpyGlass, Boston Scientific Inc. Massachusetts, USA) consists of a single disposable 10.5 Fr scope, which can be passed through a duodenoscope. This scope can

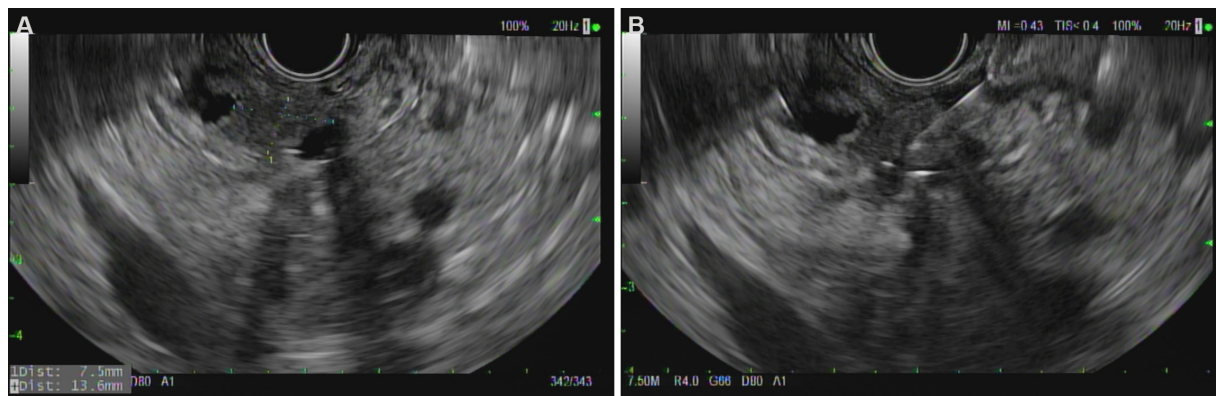


Figure 2. Endoscopic ultrasound demonstrating (A) mass in the distal bile duct in a patient with cholangiocarcinoma (B) fine needle aspiration of the mass.

be passed over a guidewire into the bile duct enabling direct visualization, with the ability to perform suction, irrigation and biopsies with specialized forceps (SpyBite)^[49]. The presence of an obvious mass (nodular or papillary), abnormal blood vessels which are dilated and tortuous, irregularity in the surface can be predictive of malignancy [Figure 3]. Pereira *et al.*^[50] in their retrospective study showed a visual accuracy of 95.1% for the diagnosis of malignancy with a sensitivity of 100% and specificity of 89.5%. The SpyBite's accuracy was 80.5% with a sensitivity of 64% and specificity of 100%. Evaluation by cholangioscopy changed the Bismuth classification in 42% of patients compared to imaging prior to the study. Other studies have shown a higher sensitivity for SpyBite up to 86%^[51,52]. Varadarajulu *et al.*^[53] in their retrospective study of 31 patients with indeterminate biliary strictures, demonstrated that the sensitivity could be increased to 94% using rapid on-site examination with cytology^[54]. A randomized controlled trial (RCT) by Bang *et al.*^[55] comparing patients undergoing cholangioscopy guided biopsies for indeterminate biliary strictures with onsite vs offsite processing techniques demonstrated similar diagnostic accuracy, sensitivity and specificity for both techniques, but the median number of biopsies to establish diagnosis was lower in the onsite group.

Studies have reported higher morbidity and rate of complications with cholangioscopy with up to five times higher rates of cholangitis in these patients. A meta-analysis including more than 2000 patients reported an adverse event rate of 7% with a serious adverse event rate of 1%^[56]. The role of direct cholangioscopy in the diagnostic algorithm [Figure 4] for biliary cancers is still being investigated given the complexity, availability, procedural duration, costs, and complications. It is a valuable tool for the investigation of indeterminate biliary strictures with prior ERCPs inconclusive for malignancy when the clinical suspicion is high.

Treatment

Therapy for malignant biliary strictures depends primarily on the level of obstruction (hilar vs. distal) and if the malignancy is resectable or not. The treatment goal for biliary malignancies is providing a surgical cure if the cancer is resectable or promoting biliary drainage in unresectable cancers. With advances in the field of interventional endoscopy and ERCP, biliary drainage can be achieved in most patients thus improving the quality of life.

Resectable cancers

Hyperbilirubinemia was thought to be associated with poorer surgical outcomes and hence earlier studies focused on biliary drainage pre-operatively to reduce the risk by the placement of biliary stents endoscopically^[57]. More recent data in the form of RCT have not shown any benefit in mortality for patients

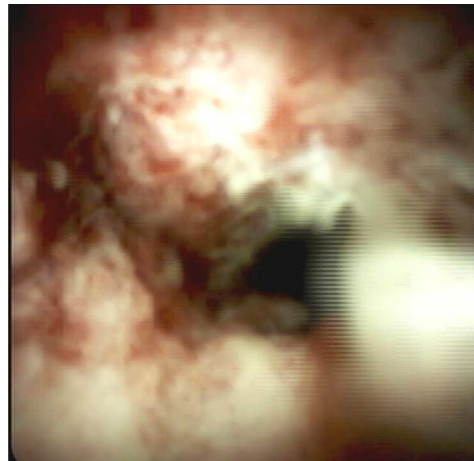


Figure 3. Spyglass cholangioscopy demonstrating infiltrative mass in the bile duct with abnormal vasculature and friable mucosa in a patient with cholangiocarcinoma.

who underwent pre-operative drainage, but also demonstrated an increase in complications post-operatively for these patients^[58,59]. Specifically, cholangitis is a clinical concern as placement of a stent for biliary drainage would increase the risk of infection in an otherwise sterile field without an ERCP. Another RCT comparing endoscopic and percutaneous transhepatic biliary drainage (PTBD) for pre-operative biliary drainage was terminated early due to higher mortality in the PTBD arm (41%) compared to endoscopic drainage (11%)^[60]. A meta-analysis by Fang *et al.*^[61] also demonstrated no mortality benefit for pre-operative biliary drainage. For distal strictures due to pancreatic cancer and asymptomatic hyperbilirubinemia, the American Society for Gastrointestinal Endoscopy recommends against routine preoperative biliary drainage. Endoscopic biliary drainage pre-operatively should be reserved for patients who have cholangitis, significant symptoms due to obstruction like pruritis and for those patients undergoing neo-adjuvant chemotherapy in order to bring the higher bilirubin levels down prior to chemotherapy^[62]. It is also ideal to delay the surgery a few weeks after biliary drainage if able, for the hepatic function to normalize, to improve the post-operative outcomes. For distal cancers, pancreaticoduodenectomy or Whipple's procedure is the treatment of choice. For intra-hepatic tumors, resection of the tumor with negative margins with or without portal lymphadenectomy is generally performed. For perihilar tumors, hepatic lobectomy or trisectionectomy along with resection of the extra-hepatic bile duct and gall bladder with a Roux-en-Y hepatico-jejunostomy is performed.

Unresectable cancers

Most CCA, close to 70%-80%, are unresectable at the time of diagnosis and endoscopic procedures in these patients are mainly palliative to decompress the biliary tract and improve quality of life but have no mortality benefit. The endoscopic options available are ERCP with biliary stenting which is the primary palliative modality, EUS guided biliary drainage, endoscopic radiofrequency ablation or photodynamic therapy (PDT). Percutaneous biliary drainage (PTBD) is also an approach used for palliation. It is generally used for segmental biliary obstruction due to tumors in the intra-hepatic bile ducts where endoscopic therapy may not be feasible or in selected patients with hilar CCAs. A study by Lee *et al.*^[63] evaluated outcomes for PTBD and endoscopic drainage for various types of Bismuth classification lesion. For type I and II lesions, there was no difference in the stent patency rates between both the groups for metal stent placement using either method. The best results were seen with endoscopic drainage in Bismuth type III lesions and PTBD for Bismuth type IV lesions^[63]. Several studies have been performed comparing these two techniques of biliary drainage, including meta-analyses and results have shown that both techniques are



Figure 4. Diagnostic algorithm for malignant biliary stricture. US: Ultrasonography; CT: computed tomography; MRI/ MRCP: magnetic resonance imaging/magnetic resonance cholangiopancreatography; CBD: common bile duct; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; FNA: fine needle aspiration; IDUS: intraductal ultrasound.

comparable in efficacy with certain advantages to each technique, but lesser morbidity and patient comfort with endoscopic drainage. PTBD is generally reserved when endoscopic biliary drainage fails^[64].

ERCP stenting

Endoscopic stenting has shown to be superior to surgical decompression with a bypass with less morbidity and mortality in multiple studies, but the surgical bypass is more durable as endoscopic drainage has a higher risk of biliary obstruction requiring repeat procedures^[65,66]. Decompression with stenting is performed with ERCP and placement of a metal or plastic stent. In general, self-expandable metal stents (SEMS) are primarily used for decompression in MBO. Several studies have shown a lower rate of stent dysfunction and lower re-intervention rates with SEMS, mainly for extrahepatic tumors with strictures^[67,68]. A meta-analysis by Zorrón Pu *et al.*^[69] showed stent dysfunction rates of 22% for SEMS compared to 47% for plastic stents with a stent patency duration of 250 days in comparison to 124 days with plastic stents. Moole

et al.^[70] in their meta-analysis showed the median stent patency duration to be 167.7 days for SEMS while only 73.3 days for plastic stents, with lower rates of cholangitis in SEMS. Sangchan *et al.*^[71] in their RCT demonstrated a survival benefit for patients with SEMS compared to plastic stents but other studies have shown mixed results. Thus, the consensus is the use of SEMS for MBO, especially for distal strictures. The role of plastic stents for distal MBO is typically considered in patients with a life expectancy of fewer than 3 months.

Type of SEMS

Biliary SEMS come in diameters of 6, 8 and 10 mm with lengths from 4 to 10 cm. They can be of 3 types: fully covered (FCSEMS), partially covered (PCSEMS) or uncovered (USEMS). These stents are made from various materials and can be present with or without anti-migration valves and anti-reflux mechanisms^[72]. They each have their own set of advantages and disadvantages. Generally, FCSEMS are more expensive and have higher rates of migration and reflux of duodenal contents, but they are easily removable^[73]. They have also demonstrated higher rates of cholecystitis if the stent is placed across the cystic duct^[74]. In comparison, USEMS have higher rates of tissue ingrowth and difficult to remove but have lower rates of migration. Both have comparable patency rates. The choice of SEMS in patients depends primarily on the level of biliary obstruction, distal MBO vs. proximal MBO due to hilar strictures, and whether removability may be important (e.g., indeterminate strictures).

For distal unresectable MBO, FCSEMS or UCSEMS are the primary options. Several studies have been performed comparing these two stents with conflicting results. Lee *et al.*^[75] in their retrospective study showed a higher rate of tissue ingrowth with obstruction in USEMS (76% vs. 9%) but stent migration was more common in FCSEMS (36% vs. 2%). In contrast, Conio *et al.*^[76] in their RCT of 158 patients found higher rates of stent migration as well as stent occlusion in FCSEMS. Majmudar *et al.*^[77] demonstrated higher rates of cholecystitis by 15% for FCSEMS when compared to USEMS but another study by Isayama *et al.*^[73] showed no statistically significant difference between the two stents for cholecystitis in distal MBO. Thus, there is no consensus on the ideal type of stent to be used for distal MBO. The choice of stents should be individualized for every patient, depending on other clinical factors, life expectancy, possible need for removal and plan for chemoradiation.

For malignant hilar strictures, the choice of stents are either plastic or USEMS. Plastic stents are generally preferred for palliative stenting to relieve the biliary obstruction. FCSEMS are generally not preferred as they can cause blockage of the contralateral intrahepatic duct system. Several studies have investigated unilateral (left or the right duct system) or bilateral stenting. De Palma *et al.*^[78] in their RCT of 157 patients with hilar obstruction, comparing unilateral and bilateral stenting, demonstrated superior stent insertion rates with unilateral stenting (88.6% vs. 76.9%, $P = 0.04$) and higher complication rates with bilateral stenting (26.9% vs. 18.9%, $P = 0.03$) on intention-to-treat analysis. A meta-analysis by Aghaie Meybodi *et al.*^[79] of 1300 patients with hilar strictures demonstrated comparable efficacy and safety for unilateral and bilateral stenting. Although in theory, bilateral stenting would make sense in draining more volume of the liver, studies have not shown the difference in survival, efficacy or complication rates between these two techniques. The principle of biliary stenting is to aim for drainage of at least 50% of the volume of the liver as studies have demonstrated a decreased risk of cholangitis and improved survival with it. Obtaining imaging prior to and after biliary stenting may provide information on the effective liver volume that is drained.

Radiofrequency ablation

Radiofrequency ablation (RFA) involves the administration of thermal energy to the malignant tumor causing tissue destruction with necrosis. The indications for the use of RFA are primarily focused on

relieving obstruction of the bile duct and tissue ingrowth in the SEMS^[80]. The technique involves advancing the catheter over a guidewire towards the target site. There are two catheters primarily used for this purpose: Habib Endo Bipolar Radiofrequency ablation catheter (Boston Scientific, USA) and Endoluminal Radiofrequency Ablation (Taewoong Medical, South Korea). Case series have reported improved survival and stent patency rates in patients who had RFA followed by SEMS in comparison to only SEMS. Increased incidence of adverse events such as cholangitis, pancreatitis and cholecystitis have been noted^[81]. There is currently a need for RCTs to demonstrate survival benefits with RFA.

Photodynamic therapy

PDT has been described as an endobiliary treatment for CCA, mainly hilar CCA. The treatment consists of injection of a photosensitizing substance combined with irradiation of a laser at a specific wavelength^[82]. This results in necrosis of the tumor cells by causing a disturbance in the vasculature and release of cytotoxic enzymes from lysosomes causing degradation of cell membranes. Cheon *et al.*^[83] in their non-randomized prospective study compared patients undergoing PDT and stenting with those undergoing only biliary stenting for drainage. The median survival duration was longer in the PDT group compared to stenting-only group (588 days *vs.* 288 days, $P = 0.01$)^[83]. There are published RCTs comparing PDT plus stenting with biliary stenting only. Ortner *et al.*^[84] in their study on non-resectable CCA, demonstrated a mortality benefit (median of 493 days *vs.* 98 days, $P < 0.01$) with improvement in quality of life. Zoepf *et al.*^[85] in their RCT of 32 patients with bile duct cancer, demonstrated a longer duration of survival (21 months *vs.* 7 months, $P = 0.01$) in the PDT group, but there were also higher rates of post-intervention cholangitis. Reports of bacterial cholangitis, liver abscesses and photo-toxicity to the skin ranging from 0%-25% have been published in clinical studies. One major limitation of PDT is its availability, being restricted only to large tertiary care centers, and phototoxicity to the skin and eyes. PDT has demonstrated good efficacy by the destruction of superficial layers of the bile duct tumors up to 5 mm with significantly less efficacy when tumor extension is beyond 7 to 9 mm depth^[86]. Currently, the indications for PDT are sclerosing variant or superficial spreading type without mass variants of CCA without any distant or nodal metastasis. Factors associated with the survival of patients have been studied for PDT. The presence of lower serum albumin pre-treatment, visible mass on imaging and longer duration between diagnosis and PDT treatment are associated with poorer survival rates while lower pre-treatment bilirubin level and multiple PDT treatment sessions have demonstrated improved survival rates^[87,88].

EUS guided biliary drainage

When ERCP-guided biliary stenting failed, PTBD used to be the alternative treatment of choice. The advancement in the field of interventional EUS has provided another approach for internal biliary drainage. There are three different techniques for biliary drainage with EUS: (1) drainage of the intrahepatic ducts by hepatico-gastrostomy (HGS); (2) drainage of the extrahepatic CBD by choledocho-duodenostomy (CDS); and (3) EUS guided rendezvous procedure. In hepatico-gastrostomy, drainage is achieved by accessing a dilated biliary radical mainly in the left hepatic duct system followed by dilation of the tract and placement of a FCSEMS from the liver ducts to the gastric lumen^[89]. In CDS, access to the CBD is achieved from the duodenal bulb followed by placement of a FCSEMS^[90]. Drainage can also be achieved by placement of a metal stent in the gall bladder through the gastric antrum or duodenal bulb, if the cystic duct is patent^[91]. The rendezvous procedure involves placement of a guidewire with the help of EUS guided access to the CBD and through the papilla, and papillary cannulation achieved with the help of the duodenoscope over or next to the guidewire. Both RCT data and meta-analyses have shown no difference in efficacy or safety comparing HGS and CDS and the choice of approach should depend on the patient's anatomy^[92,93]. Recent studies have shown EUS-BD to be a superior option when compared to PTBD with lower rates of complications^[94].

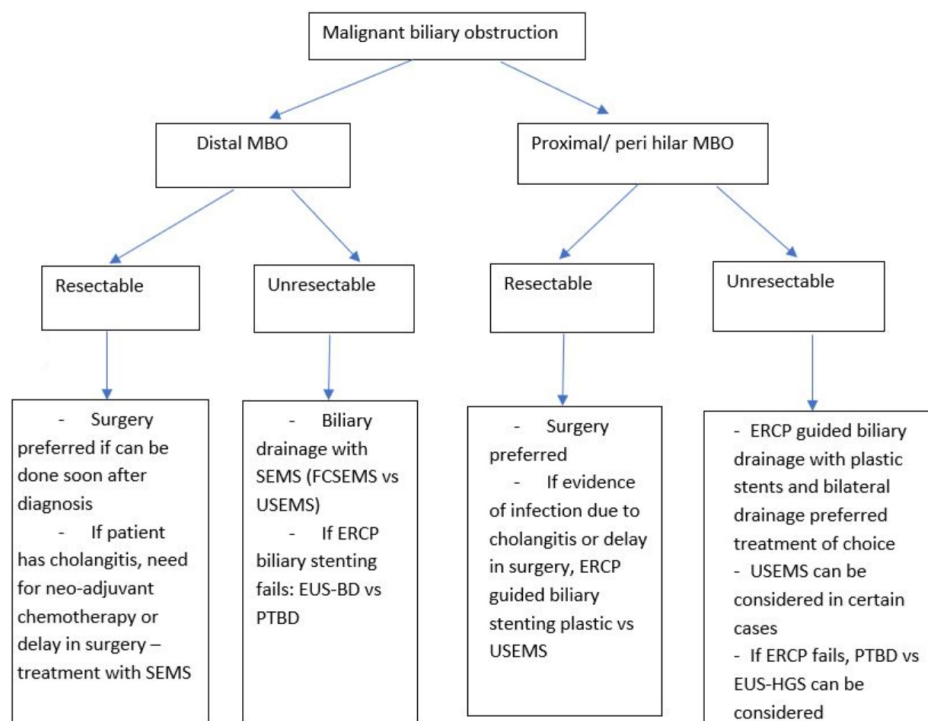


Figure 5. Treatment algorithm for management of malignant biliary obstruction. MBO: Malignant biliary obstruction; SEMS: self-expanding metal stents; FCSEMS: fully covered self-expanding metal stents; USEMS: uncovered self-expanding metal stents; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; BD: biliary drainage; PTBD: percutaneous transhepatic biliary drainage; HGS: hepaticogastrostomy.

CONCLUSION

A diagnosis of biliary malignancy should be pursued in patients demonstrating features of biliary obstruction and elevated liver enzymes in the appropriate clinical setting. The diagnostic algorithm involves obtaining tumor markers and imaging for evaluation of the biliary tract prior to tissue sampling with endoscopic techniques - EUS or ERCP. ERCP-guided brushings and forceps biopsies are the most common modality for diagnosis, but cholangioscopy guided direct biopsies can be obtained for indeterminate biliary strictures with prior inconclusive ERCPs. Treatment is mainly aimed at biliary drainage with trans-papillary stenting in unresectable cancers as a palliative measure, with metal stents generally preferred for distal cancers and plastic stents for more proximal tumors. For resectable cancers, up-front surgery is generally preferred unless it is delayed for neo-adjuvant chemotherapy or in patients with cholangitis, in which case ERCP with stenting should be performed [Figure 5]. Among SEMS, there are no data to demonstrate the superiority of one type over the other and hence decisions should be individualized to the patient. Recent advances in interventional EUS can help with both diagnoses and for biliary drainage in patients with failed ERCP or with inaccessible papilla. Despite the significant progress in this field, there are still some deficiencies that need to be addressed and further research with RCTs is needed.

DECLARATIONS

Authors' contributions

Conception and design, data acquisition, drafting of manuscript, revision of manuscript: Thoguluva Chandrasekar V

Conception and design, critical review, revision of manuscript: Faigel D

Availability of data and material

Not applicable.

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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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Case Report

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Laparoscopic mesh repair of strangulated groin hernias requiring bowel resection

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Abstract

No robust data support laparoscopic mesh repair in strangulated groin hernias. This is a retrospective review over 6 years of a single surgeon's experience treating strangulated groin hernias using the laparoscopic trans-abdominal preperitoneal mesh repair with concomitant bowel resection through a periumbilical incision. Nine patients presented with incarceration of 2 inguinal and 7 femoral hernias. The median age was 83 years (IQR 68, 85). One patient was male, all were Caucasian, and 5 were ASA 3-4. The median hospital length of stay was 6 days (IQR 4, 7). There were no known hernia recurrences or mesh infections at 30 days. Laparoscopic repair necessitates mesh placement, and doing so in a clean-contaminated setting is acceptably low risk. Laparoscopy permits better assessment of bowel viability compared to open repair and enables mesh coverage of both the inguinal and femoral spaces.

Keywords: Clean-contaminated mesh, strangulated hernias, trans-abdominal preperitoneal

INTRODUCTION

Strangulated groin hernia is a relatively rare condition that requires emergency surgical treatment. Groin hernia repair, however, is extremely common. Various techniques exist via open and minimally invasive approaches. The literature shows that laparoscopic repair for elective hernias has many benefits over the open approach. Similar complication and recurrence rates are seen, but there typically is less pain and time



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needed for recovery^[1,2]. Strangulated groin hernias present a more unique problem in which the contents of the hernia may be compromised and nonviable. Because of this, repair of these hernias was traditionally done via an open approach, partly due to the difficulty in safely reducing herniated contents laparoscopically. The other reason relates to the risk of leaving prosthetic material in a potentially infected field, therefore increasing surgical site infection risk and warranting open tissue repair^[3]. Despite this dogma, laparoscopic repair with mesh has been documented as a safe approach for strangulated groin hernias^[4-8]. However, there are no robust data to support this. We present our experience with the use of laparoscopic repair of strangulated groin hernias with concomitant bowel resection to support that this is a safe and effective option.

CASE REPORT

Methods

This is a retrospective review of a single surgeon's operative experience from January 2013 to July 2019 of all patients presenting with strangulated inguinal or femoral hernia who underwent laparoscopic transabdominal preperitoneal repair with small bowel resection. Demographic, perioperative, and short-term outcomes were reviewed, and descriptive statistics were performed (Microsoft Excel, 2019).

Results

Nine patients underwent laparoscopic mesh repair and small bowel resection for strangulated inguinal or femoral hernia over 6 years. All patients initially presented to the emergency department (ED). Hernias were repaired laparoscopically with a trans-abdominal preperitoneal (TAPP) approach with Bard 3DMax™ light mesh and secured with Covidien 5 mm Protack™, which is our preferred approach. Four tacks were used to secure the mesh in 8 cases, and one required 6 tacks. All patients had an open small bowel resection through a small periumbilical incision at the laparoscopic port site.

Diagnosis was made clinically in one patient and the remainder underwent computed tomography in the emergency department prior to evaluation by a surgeon. One patient with end-stage dementia was initially elected for hospice care and after 48 h, the family decided to pursue surgery. Three patients had attempted hernia reduction in the ED, and one was successfully reduced, but reincarcerated and was repaired 6 h after presentation. The remainder were taken to the operating room within 4 h of presentation. Two hernias were direct inguinal and seven were femoral. One of the femoral hernias was recurrent, and one patient had bilateral femoral hernias, only one of which was incarcerated; both were repaired [Table 1]. In two cases, the surgeon was consulted intraoperatively by other surgeons that were on call.

The median age was 83 years (IQR 68, 85). One was male and all were Caucasian. Interestingly, none were diabetic. The median BMI was 20.97 kg/m² (IQR 19.93, 22.08). Five patients were ASA 3-4. Postoperative median hospital length of stay was 6 days (IQR 4, 7). Three patients were discharged to a skilled nursing facility, while the rest were discharged home. One patient developed a small deep pelvic abscess treated with CT-guided aspiration and antibiotics. Two patients were lost to follow up. There were no known hernia recurrences or mesh infections at 30 days, nor were any identified during the time of chart review. Four patients were deceased at time of chart review, and the one who died within 90 days postoperatively was the same patient that initially chose hospice [Tables 1 and 2].

DISCUSSION

Hernias of the groin are common, but strangulated groin hernias are relatively rare. The risk of strangulation is higher in the case of femoral hernias. The risk of strangulation in inguinal hernias is documented as 2.8% at 3 months, increasing to 4.5% at 2 years. Femoral hernias, on the other hand, carry a

Table 1. Hospital course of patients presenting with strangulated groin hernias repaired by trans-abdominal preperitoneal mesh repair with concomitant small bowel resection

Pt	Reduced in ED	Hernia type	Diagnosis	Hospital course	LOS, days	Discharge location	30-day outcomes	F/u	Antibiotics
A	Not attempted	Strangulated right femoral	CT	Ileus, TPN	7	Home	No recurrence, infection or readmission	Yes	Preop
B	Attempted, not reduced	Strangulated left direct inguinal	Clinical	Ileus, TPN, urinary retention, pelvic abscess treated with aspiration & trimethoprim-sulfamethoxazole	12	Home	No recurrence, infection or readmission	Yes	5 days postop
C	Attempted, not reduced	Strangulated left femoral	CT	Uneventful recovery	5	SNF	No recurrence, infection or readmission	Yes	Preop
D	Attempted, not reduced	Strangulated left femoral	CT	Fall from bed, right face hematoma	4	Home with home health	No recurrence, infection or readmission	Yes	Preop
E	Not attempted	Strangulated left femoral	CT	<i>Clostridium difficile</i> diarrhea, treated with metronidazole	17	SNF	Readmitted within 30 days for MRSA cellulitis on upper extremity	No	24 h postop
F	Not attempted	Strangulated right femoral	CT	Oral thrush, ileus, pulmonary edema, HAP, urinary retention	7	SNF	No recurrence, infection or readmission	No	24 h postop
G	Not attempted	Strangulated right direct inguinal	Clinical, CT	Ileus	6	Home	No recurrence, infection or readmission	Yes	Preop
H	Not attempted	Strangulated recurrent left femoral	CT	Uneventful recovery	2	Home	No recurrence, infection or readmission	Yes	Preop
I	Not attempted	Strangulated right femoral, non-incarcerated left femoral	CT	Uneventful recovery	4	Home	No recurrence, infection or readmission	Yes	Preop

Pt: Patient; ED: emergency department; LOS: length of stay; F/u: follow up; CT: computed tomography; TPN: total parenteral nutrition; HAP: hospital acquired pneumonia; SNF: skilled nursing facility; MRSA: methicillin resistant *Staphylococcus aureus*.

3-month strangulation risk of 22% and 21-month risk of 45%^[9]. Laparoscopic and open approaches exist for repair of strangulated hernias. Although laparoscopic repair necessitates placement of mesh, doing so in a clean or clean-contaminated setting is considered acceptable. Furthermore, laparoscopy provides the ability to better assess bowel viability as compared to an open anterior repair^[10], and it permits mesh coverage of both the inguinal and femoral spaces. This study adds to the literature on the safety of the laparoscopic approach.

There is no clear consensus on the best surgical approach for repairing strangulated groin hernias, but many reports have demonstrated laparoscopic repair as a safe option. Matsuda *et al.*^[4] performed a retrospective review of patients with acute strangulated hernia who either underwent open anterior repair or laparoscopic TAPP repair. There were no recurrences in either group, and complication rates were similar. While TAPP took longer to perform, the associated hospital stay was shorter^[4]. Chihara *et al.*^[5] prospectively followed patients with incarcerated or strangulated groin or obturator hernias who underwent either laparoscopic or open repair. In the laparoscopic group, one patient had conversion to a laparotomy, and 7 patients had a second-stage TAPP repair performed after bowel repair or resection. There were no instances of mesh infection in the laparoscopic group, but one patient did suffer mesh infection in the open group. While the laparoscopic method again took significantly longer, it also displayed a decreased postoperative complication rate and hospital length of stay^[5].

Table 2. Patient demographics and comorbidities of patients presenting with strangulated groin hernias repaired by trans-abdominal preperitoneal mesh repair with concomitant small bowel resection

Pt	Age, years	Sex	ASA	Smoker	BMI	Cardiac history	Pulmonary history	Other history	Deceased	Cause of death
A	57	F	2	Current	20.80	HTN	COPD		No	
B	68	F	2	Never	20.97				No	
C	83	F	3	Former	22.08	HTN		CVA	Yes	Died in hospice from upper gastrointestinal hemorrhage 5 years later
D	93	F	3	Never	22.03	HTN, CAD, pacemaker, CABG			Yes	Died 2 years postoperatively, cause not listed
E	92	M	4	Unknown	18.64	HTN, CAD, pacemaker, IHD	COPD, pulmonary HTN	Dementia	Yes	Readmitted 6 weeks postoperatively and died from CHF exacerbation and MRSA cellulitis
F	85	F	4	Current	19.93	HTN, atrial fibrillation	COPD		Yes	Died 3 years later from complications from CVA
G	62	F	1	Never	22.50				no	
H	75	F	2	Former	26.25	HTN			No	
I	85	F	3	Never	17.47				No	

Pt: Patient; ASA: American Society of Anesthesiologists physical status classification; BMI: body mass index; F: female; M: male; HTN: hypertension; CAD: coronary artery disease; CABG: coronary artery bypass graft; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; CHF: congestive heart failure; MRSA: methicillin resistant *Staphylococcus aureus*.

This case series supports the use of laparoscopic TAPP repair for strangulated groin hernias. In our experience, TAPP is a safe approach with concomitant bowel resection, as long as frank perforation with gross spillage of succus does not occur. Similar recurrence rates are generally seen between the open and laparoscopic approaches, and some argue decreased complications with the laparoscopic method. TAPP gives the ability to reduce the hernia under direct visualization while permitting assessment of bowel viability in real time. Further, in the laparoscopic approach, the mesh covers the direct, indirect and femoral spaces, theoretically preventing future herniation through the other spaces, which is not always the case in open approaches.

Ultimately, the surgeon should choose the repair with which he or she is most comfortable and familiar. As surgeons become more facile with laparoscopic repair, it should be considered for incarcerated hernias due to the benefits of more complete bowel assessment for viability, reduced pain, time to recovery, and hospital stay.

Conclusion

Strangulated groin hernia is a rare medical emergency that warrants rapid operative repair. The best method of repair in this setting is not well defined, but laparoscopic repair with mesh appears to be a safe and effective option, even when bowel resection is performed. The authors support the use of laparoscopic repair if it fits the experience and comfort of the surgeon.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Smith A, Hope W, Fox S

Performed data acquisition, as well as provided administrative, technical, and material support: Bilezikian J, Hope W

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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Original Article

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Retrospective study assessing the learning curve and the accuracy of minimally invasive robot-assisted pedicle screw placement during the first 41 robot-assisted spinal fusion surgeries

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Abstract

Aim: The purpose of this study was to assess the learning curve and the accuracy of robot-assisted pedicle screw placement in the first 41 cases.

Methods: This retrospective study investigated the first 41 patients undergoing spinal fusion, whereby 250 pedicle screws were inserted with robotic assistance in a private hospital by a single surgeon. The pedicle screw accuracy was evaluated by computed tomography scan by an orthopedic surgeon according to the Gertzbein and Robbins classification. Planning time and screw placement time were noted. In addition, data about any screw malposition, a return to the operating theatre, and intraoperative repositioning were collected. The data were analyzed with Microsoft Excel.

Results: The results show a high degree of accuracy (98%) of pedicle screw placement with a minimally invasive robot-assisted spinal fusion with no screw malposition requiring a return to the operating theatre. The learning curve improved with time, reaching a plateau at around 25 cases.



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Conclusion: This study shows a high degree of accuracy of pedicle screw placement with the robot and it shows a surgeon's improved experience with the robot with time. Further comparative studies are needed to better assess the robot's accuracy and its future in spine surgery.

Keywords: Minimally invasive surgical procedures, bone screws, vertebrae, robotics

INTRODUCTION

Pedicle screws remain the primary mode of fixation providing adequate stabilization for facilitating fusion in spinal procedures. Freehand pedicle screw insertion remains a challenging procedure owing to the many important structures near the pedicle, such as the spinal cord, nerve roots, and associated vessels. Complications such as neurological deficits and vascular injuries secondary to misplaced pedicle screws are prevalent with an incidence of 1%-54%^[1].

Moreover, complex deformities such as scoliosis and morphologic conditions such as dysplastic vertebral pedicles make screw placement challenging. The introduction of fluoroscopy has improved accuracy and facilitated the emergence of minimally invasive surgery procedures, but it has also given rise to increasing concerns of radiation exposure to the surgical team^[2]. Recent availability and acceptance of computer-assisted navigation techniques have minimized the risk of radiation exposure to the surgical team and improved the accuracy of screw placement, but this is largely dependent on the surgeon's expertise and knowledge of anatomy^[3].

The navigation-assisted spinal robotic system (ExcelsiusGPS®, Globus Medical, Inc., Audubon, PA) used in this study is a floor-mounted guidance arm system that allows for placement of pedicle screws along the preplanned trajectory with real-time navigation guidance. Initial results show increasing accuracy of screw placement in prone and lateral position surgeries, allowing for reduction in surgical time for anterior interbody fusion with posterior instrumentation and overall radiation exposure to the surgical team^[4]. However, the learning curve of this new technique needs further evaluation.

We aimed to evaluate the learning curve and describe our experience of using the ExcelsiusGPS robot in the setting of prone and lateral position surgeries, emphasizing the surgeon's experience with planning, accuracy of implant insertion, and radiation exposure incurred in our cases.

METHODS

Patient selection

The first 43 consecutive patients were evaluated, operated by a single surgeon experienced in the use of stereotactic navigation, using the ExcelsiusGPS® (Globus Medical, Inc., Audubon, PA) at a single institution from April 2019 to February 2020. All consenting patients more than 18 years of age were included irrespective of any antecedent surgical procedures. Written informed consent was obtained from all patients. All data were obtained in the outpatient clinic with follow up period of at least one year. Two cases were removed from the study cohort due to technical malfunction in the robot. The robot was successfully used in the other 41 cases. The patient demographic data (age, sex, and BMI) were recorded. Patient position, image acquisition protocol, total time of robot use, planning time for each case, and radiation exposure were noted immediately after the procedure. Two patients underwent scoliosis deformity correction. The rest were one-, two-, or three-level interbody fusions.

Biplanar fluoroscopy was used to check the position of the screws after placement and any unacceptable screws were revised immediately and noted. Postoperatively erect radiographs were taken to check on the construct. Follow up was planned using our standard protocol with X-ray radiographs at one, three, and twelve months postoperatively and computed tomography (CT) scans at six months postoperatively of instrumented levels for all patients.

Analysis

The accuracy of pedicle screw placement was determined as grades (Grade A, 0 mm; Grade B, 0-2 mm; Grade C, 2-4 mm; Grade D, 4-6 mm; and Grade E, > 6 mm) based on the 2 mm incremental system according to CT scans at six months developed by Gertzbein and Robbins^[5]. The number of screw breaches was recorded for each group. All revised screws were considered as inaccurate. All other screws were considered for analysis irrespective of intraoperative change of trajectory or freehand placement of screws using the ExcelsiusGPS navigation system. The number of acceptable screws divided by the number of total screws placed with robotic navigation resulted in an accuracy percentage for this study.

Surgical technique

Patients were positioned prone or lateral. The position was determined based on the surgeon's preference and the surgical procedure planned. The patients who underwent posterior only instrumentation was positioned prone on the Jackson table. The surgical field was prepped and draped in the usual sterile fashion allowing access to bilateral posterior superior iliac spine (PSIS) in all cases. The ExcelsiusGPS® fiducial marker [called the dynamic reference base (DRB)] was placed in the right PSIS via a small stab incision during prone position and in the left PSIS in the single lateral position. In cases where an open incision was utilized, the DRB was mounted on the spinous process clamp attached to the lower most spinous process not considered in the construct. The intraoperative CT fixture (ICT) was attached to the fiducial marker, in a plane parallel to the floor and just above the patient's skin over the area of interest.

Patients undergoing OLIF procedure in conjunction with posterior instrumentation were positioned in the left lateral decubitus position over a flat top table and taped in the usual fashion to allow tilting of the table without allowing any patient movement intraoperatively. The surgical field was prepped and draped widely allowing access to the left Iliac crest and PSIS. The DRB was placed on the left PSIS, while the surveillance marker was placed a few inches anterior to the DRB along the crest. The DRB post was tilted caudally to avoid any interference between the camera and the reference frame. The intraoperative CT fixture (ICT frame) was attached on the DRB post and placed flat over the area of interest on the patient's skin.

Imaging protocol

The ExcelsiusGPS robotic navigation platform supports three imaging protocols: preoperative CT scan, intraoperative CT scan, and intraoperative fluoroscopy.

Preoperative CT scan

The preoperative CT scan was utilized in patients undergoing instrumentation for more than five levels. The CT scan was carried out using a special protocol involving a scan in supine position with 1 mm image cuts for integration with the robotic navigation platform. In patients with preoperative CT scan, validation of landmarks was done using serial orthogonal radiographs for each level to be instrumented. The radiographs were then transferred to the robot navigation system for screw trajectory planning. The validation and verification system of the ExcelsiusGPS robot system provided alternate ghosting images of the radiographs and the CT scan during the planning phase.

Intraoperative CT protocol

Patients undergoing less than four-level instrumentation or lateral position surgery were subjected to the intraoperative CT protocol. The O-arm-2 (Medtronic Sofamore Danek Inc, Memphis, TN) was used to acquire the three-dimensional (3D) CT scan. The surgical table was raised to a height of 110 cm from the floor for easy maneuvering of the O-arm doughnut without major adjustments needed for the CT spin. The surgical field was draped circumferentially in order to maintain sterility [Figure 1]. The scan was then transferred to the ExcelsiusGPS navigation system for pedicle screw trajectory planning, which included entry point, trajectory, screw length, and screw width.

During the planning phase, axial, sagittal, coronal, and 3D reconstruction views were available for the surgeon on the navigation screen for planning of the screw trajectories. Care was taken to use the widest and longest screws possible for each pedicle [Figure 2A].

The trajectories were matched to allow as small an incision as possible. The plan was also adjusted by the surgeon for the best possible way to allow easy rod insertion and reduction of deformity based on the surgeon's experience [Figure 2B].

Time taken for planning each screw was noted. The planning time also included sterile draping of the robot arm by the assistant done simultaneously. On validation of landmarks on the DRB with those seen on the navigation screen, the reference frame ICT was then removed from the field taking care not to disturb the DRB. The robot was then wheeled into the surgical field. The robot was docked securely to the floor once all trajectories could be reached by the end effector arm. The navigated instruments, including a position tracker, drill, and navigated screw guide, were registered in the system previously by the scrub nurse. The surgeon utilized a foot pedal to bring the robotic arm to the planned screw trajectory. With the end effector in position, a stab incision was made, and a power drill was first used to cannulate the pedicle, and the screw was then placed through the stable, rigid end effector. Real-time visualization of the screw trajectory and indicators of excessive skiving force were available to the surgeon through the process of screw insertion. Once all screws were placed, the robot was undocked and removed from the surgical field and screw placement was checked on orthogonal radiographs. Any unacceptable screws were revised immediately before advancing to the next step. Rods were inserted and the construct completed. The time taken for rod insertion was excluded from the calculation. Final A-P and lateral radiographs were taken to check the construct.

Radiation exposure: The dose imparted at each scan was calculated from the dose report generated by the O-arm and converted to mSv using a uniform tissue factor of 0.015 for uniformity in calculations. Similarly, all fluoroscopy exposures were measured in milliseconds based on the readings from the C-arm.

RESULTS

The ExcelsiusGPS Spine robot guidance system was successfully used in 41 of 43 consecutive cases between April 2019 and February 2020. Two cases were abandoned due to technical reasons where the robot could not connect with the intraoperative image acquisition system. Those cases were excluded from the study. Statistical analysis was done using Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States). Fixation was done across 86 motion segments over the course of the study period. The mean age of patients was 70.9 ± 10.5 years. Thirty (60%) patients were female and 20 (40%) were male [Table 1]. The mean BMI was 29.2. Of the 41 patients, 17 patients were operated in the single lateral position; 8 patients were operated in the lateral position and then repositioned in prone position for posterior fixation; and 16 patients were operated in prone position only. Out of the 41 lumbar fusion patients, 33 had interbody fusion

Table 1. Demographics

Age (years)	70.9 ± 9.5
M/F	15/26
Total cases (n)	41
BMI	29.2 ± 5.6
Total screws for assessment	250
Total number of instrumented levels	86

BMI: Body mass index.



Figure 1. Draping of the patient when O-arm is used with DRB and ICT shown clearly. DRB: Dynamic reference base; ICT: intraoperative computed tomography.

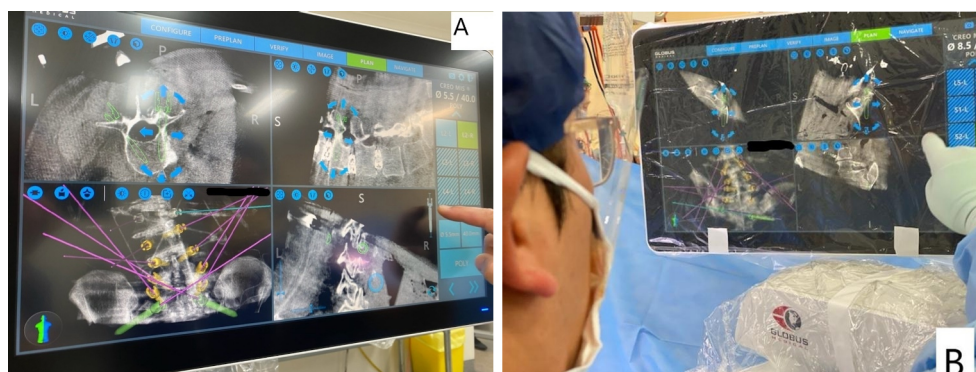


Figure 2. (A) Intraoperative planning prior to draping. (B) Intraoperative planning change with the screen draped during screw insertion.

and reconstruction. The intraoperative CT scan protocol was utilized in 38 cases. The preoperative CT scan with intraoperative fluoroscopy integration was used in three patients.

Learning curve

The patients were classified into five groups. Group A, Cases 1-9; Group B, Cases 10-18; Group C, Cases 19-26; Group D, Cases 27-32; and Group E, Cases 33-41 [Table 2]. The surgeon's learning curve was reached at

Table 2. Group characteristics of the study

Variable	Group A (9)	Group B (9)	Group C (8)	Group D (6)	Group E (9)
Screws inserted	56	60	46	38	50
Screws revised	0	1	1	0	3
Intraoperative trajectory revision	0	1	2	1	1
Unreachable trajectory	6	2	0	0	0
Grade A + B Screws	54	58	42	29	43
Grade C screws	2	2	4	9	7
Grade D, E screws	0	0	0	0	0

around Group C. In Group A, the robot could not reach all the planned screw trajectories requiring it to be repositioned in four cases. The reason was a steep sacral slope in three of these patients which was not accounted for while planning the trajectory of the screw, causing the robot arm to press on the rib cage, which obstructed achieving the final trajectory. In one other patient, the robot arm was obstructed by the operating table frame in the lateral position surgery. The unachieved trajectories were cannulated by hand using the navigation function of the robot system. No repositioning was needed in the following case groups as understanding and experience improved the trajectory planning. The surgeon showed a serial decrease in time taken to plan at each level, with an average of 4.1 min of planning per level. As this was part of the learning curve of the surgeon with this new technology, all planning and screw placement were done by the surgeon. Cases in Group E reported a longer planning time of 5.08 min per level due to educating and teaching of visiting surgeons. The two outlier cases where teaching occurred were omitted, and the scatterplot obtained showed a decrease in planning time [Figure 3].

In total, 250 screws were inserted using the robotic arm guidance to fix 86 motion segments. Fourteen screws were inserted without the use of the robot arm. The robot failed to reach its trajectory in eight screws, and they were inserted using the navigation system of the ExcelsiusGPS robot. Five screws required an intraoperative adjustment of trajectory. Five screws had to be revised. The revised screws were reported as one in Group B, one in Group C, and three in Group E. No conclusion could be derived from the increasing frequency of revised screws in the last group. However, the average insertion time of screws using the robot showed a decreasing trend [Figure 4].

The mean radiation characteristics of our experience are summarized in Table 3. The mean fluoroscopy dose in seconds per case was around 16.32 ± 13.22 s with the mean effective dose of 8.2 ± 3.74 mSv during the 3D CT scan. One patient needed a repeat scan as the CT scan was inverted and could not be validated by the robot. Fluoroscopy exposure was high in cases that required manual insertion, causing multiple shots to evaluate screw positioning. Moreover, a high radiation dose was recorded in the three cases where the preoperative CT protocol was used due to difficulty of fluoroscopy integration to match the CT images to the patient's anatomy.

Accuracy

In total, 250 screws were analyzed for accuracy on CT scan. S2 alar iliac screws as part of lumbosacral construct were deemed acceptable if they did not breach the sacral foramen or breach the pelvic wall. The overall accuracy in this study was 98%. Overall, 245 screws were deemed acceptable with 226/250 (90.4%) being Grade A + B and 24/250 (9.6%) being Grade C [Figure 5].

Five screws were revised immediately after confirming on fluoroscopy and before rod placements. Those were considered inaccurate. The inability of the robot to reach screw trajectory was high in Group A cases

Table 3. Radiation exposure recorded from the study

Mean effective dose from O-arm spin	8.2 ± 3.74 mSv
Mean fluoroscopy dose	16.32 ± 13.22 s
Mean fluoro time in preoperative CT protocol (for integration)	54 s

CT: Computed tomography.

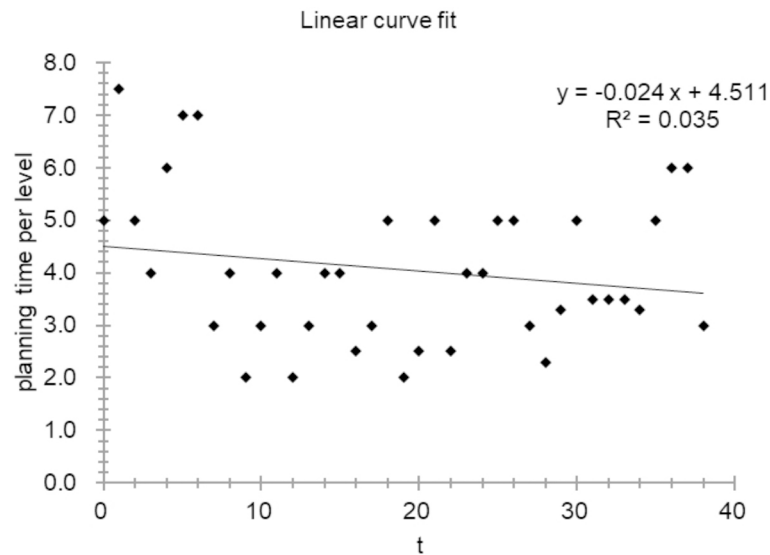


Figure 3. Scatterplot of planning time per level learning curve. The x-axis shows the case number as a function of planning time per level (results are based on 39 patients with the two outliers due to teaching purposes eliminated).

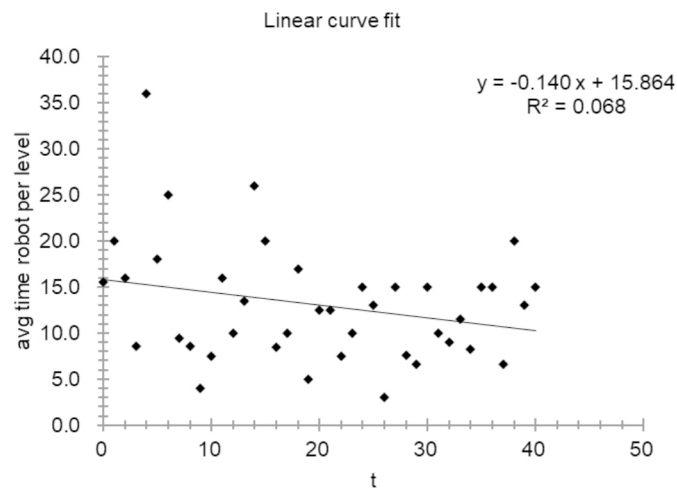


Figure 4. Scatterplot of average screw insertion time with robot as a function of cases.

(6/56) and declined in the subsequent cases. However, the last group had a rise in screw misplacements which were revised intraoperatively (3/50). This was probably due to skipping a step of validation of ICT in one instance, movement of the surveillance marker in the second instance, and error in planning in the third instance. None of the patients returned to the theatre to revise a screw.

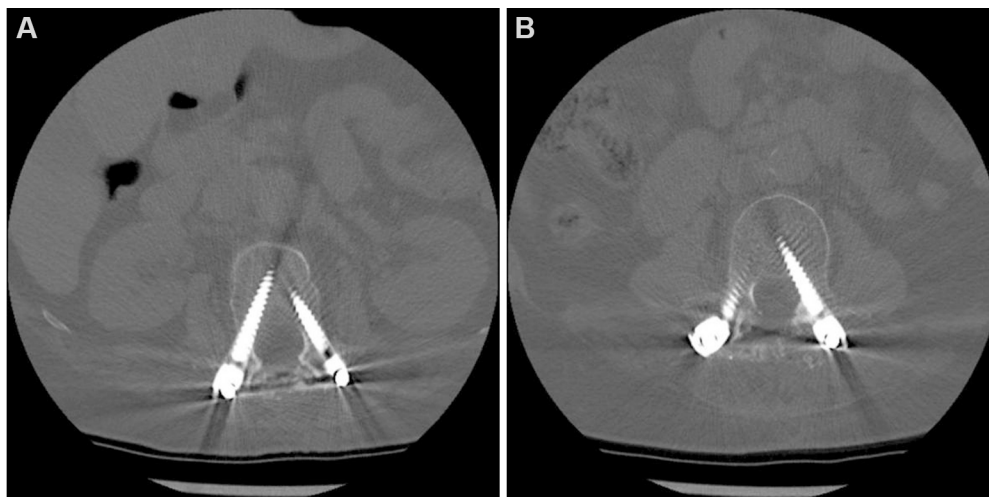


Figure 5. Axial CT scan showing: (A) Grade A on the left pedicle screw; and (B) Grade B on the right pedicle screw. CT: Computed tomography.

DISCUSSION

Robotics in spinal surgery has been developing rapidly over the last decade, designed to augment and enhance the surgeon's abilities. Freehand placement of pedicle screws requires detailed knowledge of anatomical landmarks and surgeon experience. The use of imaging technology such as fluoroscopy and intraoperative navigation has improved the safety and accuracy of pedicle screw placement over freehand techniques^[3]. The meta-analysis of 30 studies analyzing 9000 pedicle screws by Mason *et al.*^[6] concluded that traditional fluoroscopy reached an accuracy of 63.1%, two-dimensional navigation had 84.3% accuracy, and 3D navigation was most accurate at 95.5%^[7]. Many new robotic spine guidance systems are being developed, improving the safety and accuracy of pedicle screw placement. However, the learning curve of these systems has not been studied in detail. There was insufficient evidence to conclude the effectiveness of robot-assisted over conventional fluoroscopy-guided pedicle screw insertion in a systematic review by Marcus *et al.*^[8]. On the contrary, another study reported equivalent accuracy with reduced radiation exposure in robot-assisted cases compared to conventional fluoroscopy-guided surgery^[9].

Multiple studies have reported on the accuracy of robot-assisted pedicle screws using a variety of classification systems. In multiple systematic meta-analyses, it was concluded that the 2 mm incremental classification system developed by Gertzbein and Robbins has been widely accepted and used for the assessment of pedicle screw placement accuracy on CT scans^[10,11,12]. Theologou *et al.*^[13] reported good inter-observer reliability and commented on the ease of using this system. Hu *et al.*^[14] reported a high accuracy of 98.9% using the Renaissance system but used postoperative radiographs for the assessment which was a major limitation of the study. Similarly, Pechlivanis *et al.*^[15] used the Renaissance system and reported that 91.5%-98.3% of screws were placed in an acceptable position as per the Gertzbein and Robbins classification system. Keric *et al.*^[16] also reported a higher accuracy of 96.7% in the placement of 2067 screws using the assessment system described by Wiesner *et al.*^[17]. In this study, the overall accuracy was 98% using the 2 mm incremental system of CT scan. Out of 250 screws placed using the robot, five screws (2%) were revised due to unsatisfactory placement immediately after fluoroscopic confirmation. These screws were considered inaccurate. According to our assessment, 90.4% of screws (Grade A + B) were placed entirely inside the pedicle and 9.6% of screws were acceptable, being Grade C. None of the screws had any major pedicle breach or associated clinical symptoms. This was probably because the surgeon could modify the planned trajectory if there was excessive force or skiving of the drill causing malposition of screws. This helped

improve the accuracy of screw placement. Huntsman *et al.*^[4] also reported a similar high accuracy of 99% using the ExcelsiusGPS system in a study of 100 cases.

The single position lateral surgery has not gained widespread approval due to technical difficulty of cannulating a pedicle screw in the lateral position. Recent studies have reported a reduction in operative time in single position lateral pedicle screw fixation following lateral interbody fusion as compared to dual positioning without an increase in complication rates or compromised perioperative outcomes^[18-20]. The authors believe the use of the rigid robot arm of the ExcelsiusGPS system will provide a stable and accurate insertion of pedicle screws in the lateral decubitus position. The accuracy of screw placement in the subset of patients operated in a single lateral position was 97.87%, where two screws were revised out of 94 pedicle screws. A similar high accuracy of 98% was reported by Huntsman *et al.*^[4] using the ExcelsiusGPS robot system. Surgeons operating in a single lateral position surgery face the technical challenge of cannulating pedicle screws in this position and some technique-related complications; however, recent studies showed comparable results to the flip position^[18-20]. Furthermore, as the placement of S2AI screws can be challenging by the freehand technique, the robot can be used to place these screws^[21,22].

The learning curve for accurate planning and execution of screw placement was reached in Group C in this study. The time taken to plan screw trajectories saw a significant reduction in the initial period of this study. The mean time taken to plan in Group A was 5.35 min and in Group B was 3.15 min. The robot arm could not reach planned trajectories in six instances in Group A and once in Group B. The authors believe this reduction in missed trajectories was due to improved planning and increasing familiarity of the 3D interface. However, the planning time increased in the following case groups as the planning interface was utilized as an academic tool to train fellows and visiting surgeons.

Similarly, this study demonstrates a gradual reduction in screw insertion time which is comparable to other studies. Urakov *et al.*^[23] studied the mean insertion times for trainee surgeons using the older generation robotic guidance system and reported a mean time of 5.7 min per screw for percutaneous screw placement and 3.6 min per screw for freehand insertion. In our study, the initial case (Groups A and B) showed a declining trend in screw insertion time from 5.23 min per screw to 4.36 min per screw. The least amount of average time per screw was reached around the Group C mark with a mean time of 3.78 min per screw.

Radiation exposure in image-guided surgery is a significant concern to the surgical team. The use of robotic-assisted navigation has been postulated to reduce radiation exposure as compared to traditional fluoroscopy-based surgery. A recent study reported significantly lower radiation times in the robot-assisted group than in the fluoroscopy-guided group^[24]. However, the cumulative radiation exposure reported during surgery in the robot-assisted group was 93.5 ± 37.9 s, which was significantly higher than what was found in our study (16.32 ± 13.22 s). Similarly, Pennington *et al.*^[25] conducted a systematic review which found that robot-assisted surgery with preoperative CT imaging had significantly less radiation exposure than in fluoroscopy-based surgery. The researchers estimated a dose of 14-16 mSv in fluoroscopy-navigated surgeries as compared to 4.8 mSv exposure dose of intraoperative O-arm scan for CT navigation-based surgeries. This estimation, although less than the one encountered in this study (8.2 ± 3.74 mSv), can be explained by the need for a high-dose wide-view CT scan for validation of the ExcelsiusGPS system. Even though the CT radiation dose in this study was higher than that of the O-arm scan utilized in navigation-only systems (Costa *et al.*^[26]), it is significantly lower than that encountered in a fluoroscopy-based procedure. The mean fluoroscopy time reported by these researchers was 20.1 ± 17.2 s per screw, which was significantly higher than the one reported in this study (16.32 ± 13.22 s per case). Benech *et al.*^[2], in a study on the initial experience and radiation exposure using a similar robotic guidance system, reported a

fluoroscopy time of 17.6 ± 17.4 s for the entire case series, which is significantly less compared to our finding of 54 s in the group of cases operated using the preoperative CT protocol. The authors believe the complex deformity reconstruction and instrumentation at more than five levels was the reason for the higher fluoroscopy exposure in this study, as it took more than two orthogonal radiographs per level for accurate validation of anatomical landmarks for integration of the preoperative CT scan.

The use and acceptance of new technology always raises important questions regarding the development of skill and the ease of introduction of the new technique in clinical practice. Robot-assisted spine surgery faces the same challenges. All new technologies and techniques have a learning curve that a surgeon must overcome to be proficient in its use. In the authors' opinion, the learning curve for this technique lies around the 25 cases mark. The authors believe supervised training in the initial period can help reduce the learning curve for improved surgical outcomes. This study showed acceptable accuracy in the placement of pedicle screws, but, ultimately, it depends on the meticulous planning and effective execution of the plan.

Limitations

There are several limitations to this study. Even though this is a single-center study, the patients were not randomized and lacked a comparative control. Even though our study reports excellent accuracy in the placement of pedicle screws with reduced radiation exposure, robotic navigation systems are not common due to the large financial commitments involved. A larger sample size is needed to evaluate the overall effectiveness and cost-benefit analysis of this novel robotic navigation system.

In conclusion, robot-assisted spinal surgery is still in the initial stages of development but shows promise. Currently, the use of navigation-assisted robotics appears to provide safe and accurate placement of pedicle screws in prone as well as lateral single position surgery and appears superior to freehand screw placements, although detailed studies with larger sample size are needed for a conclusive determination. Radiation exposure encountered in this study was significantly less as compared to fluoroscopy-guided surgeries, especially in lateral access single position surgeries. We conclude that, with a short learning curve of 25 cases, robotic spine surgery seems to be useful in execution of complex deformity reconstructions. However, ultimately, it is up to the surgeon to effectively execute the planned procedure with the help of the robot system.

DECLARATIONS

Authors' contributions

Design of the work, writing and revising the manuscript, analysis and collection of data: Maalouly J

Collection of data and writing of the manuscript: Sarkar M

Design of the work, writing of the manuscript and supervision of the study: Choi J

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

Written informed consent was obtained from all patients.

Consent for publication

A written informed consent for publication was obtained.

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Review

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Indications of esophageal cancer for endoscopic submucosal dissection, curability, and future perspectives

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Abstract

This review considers the preferred preoperative examinations, indications for endoscopic submucosal dissection (ESD), and curative ability of ESD in patients with esophageal squamous cell carcinoma (SCC). Endoscopic evaluation by non-magnifying endoscopy followed by magnifying endoscopy is a common procedure for diagnosing invasion depth of superficial esophageal SCCs in Japan. However, endoscopic ultrasonography may increase overdiagnosis of the depth of cancer invasion, and therefore should not be performed routinely. Image-enhanced magnifying endoscopy or iodine staining is recommended for diagnosing the lateral extent of esophageal SCC. The indications for ESD include clinical T1a-epithelial/lamina propria (EP/LPM) NOMO non-circumferential lesions, clinical T1a EP/LPM NOMO circumferential lesions ≤ 50 mm, and clinical T1a-muscularis mucosae/T1b-submucosa 1 cancer (invading submucosa by ≤ 200 μ m) NOMO non-circumferential lesions. Pathological T1a EP/LPM without vascular invasion is defined as curative resection, while pathological T1a MM without vascular invasion is considered as non-curative resection, with undetermined recommendations for additional treatment. Pathological T1b cancer invading the submucosa or pathological vascular invasion-positivity is considered as non-curative resection, and additional treatment is recommended. An accurate preoperative diagnosis, appropriate indication, and adequate curability assessment based on the pathological diagnosis of resected specimens are important for effective ESD.

Keywords: Esophageal cancer, cancer invasion depth, endoscopic submucosal dissection



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INTRODUCTION

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-related death worldwide, with 572,000 new cases and 509,000 deaths in 2018^[1]. Although the incidence of esophageal adenocarcinoma is increasing rapidly in Europe and North America, esophageal squamous cell carcinoma (SCC) remains the most common histological type, accounting for 80% of all esophageal cancers worldwide^[1].

The overall survival of patients with advanced esophageal cancer remains poor, regardless of histological type. However, when diagnosed at an early stage, esophageal cancer can be cured by endoscopic submucosal dissection (ESD), surgical resection, or chemoradiotherapy. Superficial SCC is defined as cancer limited to the mucosa or the submucosa. The treatment strategy for superficial SCC of the esophagus is determined based on the preoperative diagnosis of cancer invasion depth, lateral extent of the cancer, and metastasis. The curative ability of tumor resection is usually determined by the histologic findings of the resected specimen. This review will discuss the preferred preoperative examinations, indications for ESD, and curative ability of ESD in patients with esophageal SCC.

PREOPERATIVE EXAMINATIONS

Diagnosis of cancer invasion depth

Endoscopic evaluation by non-magnifying endoscopy (non-ME) followed by magnifying endoscopy (ME) is the common procedure for diagnosing invasion depth of superficial esophageal SCC in Japan. Endoscopic ultrasonography (EUS) is also used to diagnose cancer invasion depth but is currently not used as a standard procedure because of conflicting results regarding its diagnostic accuracy^[2,3]. Although EUS is recommended for staging T1 esophageal cancer in some guidelines^[4-6] and by some experts^[7], it is not recommended in other guidelines^[8,9]. A recent multicenter study was conducted to evaluate the additional diagnostic value of EUS following non-ME+ME for differentiating superficial SCC into M/SM1 cancer (mucosal cancer/cancer invading into the submucosa by $\leq 200 \mu\text{m}$) and $\geq \text{SM2}$ cancer (cancer invading into the submucosa $> 200 \mu\text{m}$)^[10]. Additional use of EUS after non-ME+ME increased the proportion of overdiagnoses by 6.6% (21.6% vs. 28.2%, one-sided $P = 0.93$), with similarly increased tendencies for overdiagnosis in all subgroup analyses. Although the addition of EUS reduced the proportion of underdiagnoses by 4.5% (29.2% vs. 24.7%), it did not improve the accuracy of distinguishing between M/SM1 and $\geq \text{SM2}$ superficial SCCs. Overdiagnosis of the depth of invasion means that cancers potentially curable by endoscopic resection may be treated by esophagectomy, while underdiagnosed cancers may be treated by endoscopic resection, with no curative effect. An increase in overdiagnosis is considered to have a greater impact than underdiagnosis, because over diagnosed patients may receive unnecessary esophagectomy, which is more invasive than unnecessary endoscopic resection caused by an underdiagnosis. Similar results were reported in other studies evaluating the usefulness of additional EUS^[11,12]. Considering the risk-benefit balance of adding EUS, the current results suggest that EUS should not be performed routinely in patients with superficial esophageal SCC.

Diagnosis of lateral extent

The Esophageal Cancer Practice Guidelines 2017^[4] suggest that the extent of endoscopic resection is closely related to the risk of stenosis, and it is therefore “strongly recommended to evaluate the circumferential extent of the lesion preoperatively”. Image-enhanced magnifying endoscopy or iodine staining is recommended to diagnose the lateral extent of the lesion [Figure 1], with the latter allowing clear delineation of the lesion border. However, use of high concentrations of iodine solution may cause the superficial epithelium to peel off, making a subsequent diagnosis difficult, and thus iodine solution should be used at a low concentration of $\leq 1\%$.

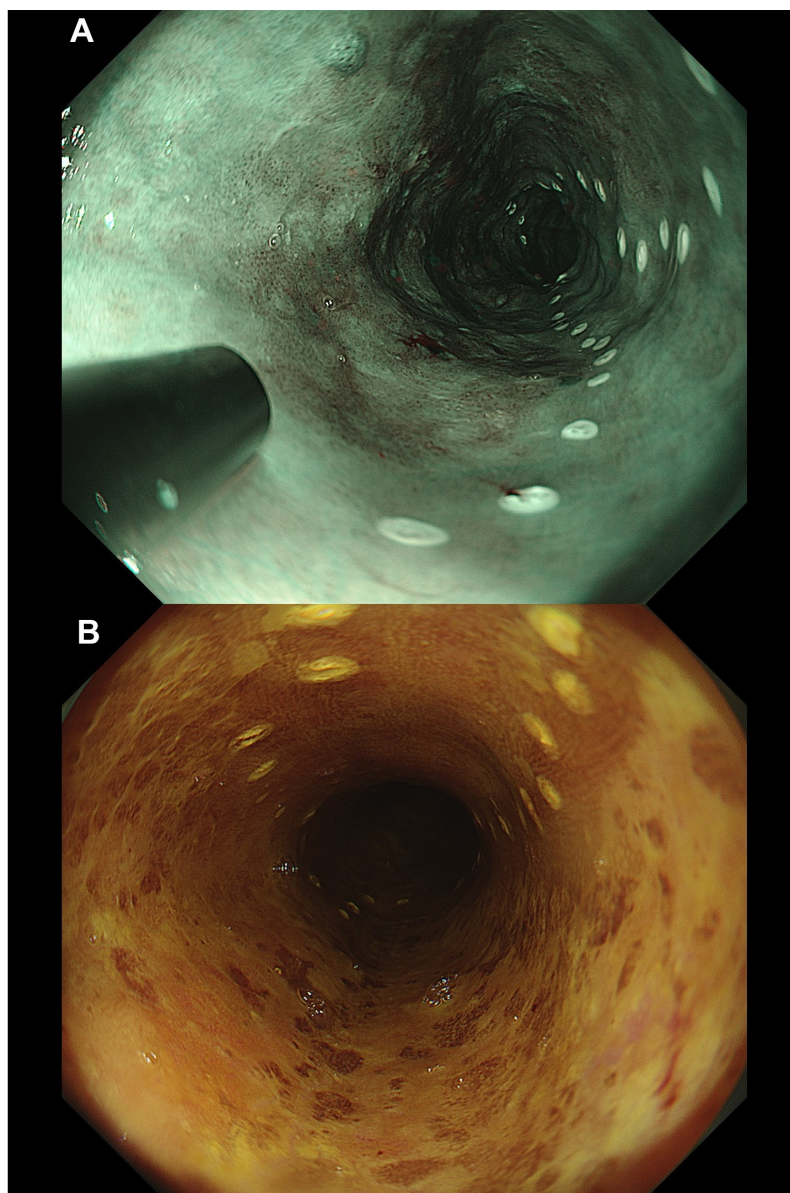


Figure 1. Diagnosis of lateral extent. (A) The lateral extent of the cancer was initially diagnosed using narrow-band imaging. (B) The lateral extent was then confirmed by iodine staining.

INDICATIONS FOR ESD [Table 1]

Cancer invasion depth

The indication for ESD in patients with T1N0M0 esophageal SCC is determined mainly based on cancer invasion depth and the lateral extent of the cancer. Clinically diagnosed (c)T1a-epithelial/lamina propria (EP/LPM) cancers are considered good candidates for ESD and are thus regarded as an indication for ESD. The committee for the Japanese ESD/endoscopic mucosal resection (EMR) Guidelines^[13] previously discussed the validity of T1a-muscularis mucosae/T1b-submucosa 1 (MM/SM1) as an indication for ESD. However, there is considerable discrepancy between (c)MM/SM1 and pathologically diagnosed (p)MM/SM1, and these should thus be treated separately. The above committee discussed the validity of (c)MM/SM1 as an indication for ESD.

Table 1. Indications for endoscopic submucosal dissection

√ Clinical T1a-epithelial/lamina propria (EP/LPM) NOMO non-circumferential lesion
√ Clinical T1a EP/LPM NOMO circumferential lesion ≤ 50 mm
√ Clinical T1a MM/T1b SM1 cancer (invading submucosa by ≤ 200 μ m) NOMO non-circumferential lesion

T1a MM/T1b SM1: T1a-Muscularis Mucosae/T1b-Submucosa 1.

Previous reports^[14-18] showed that 27.4%-55.2% of cancers diagnosed as (c)MM/SM1 before treatment were (p)EP/LPM cancers [Figure 2], for which endoscopic resection is highly likely to be curative. This indicates that the accuracy of preoperative diagnosis for (c)MM/SM1 cancers is poor, and that a considerable proportion of esophageal SCC, which is curable by ESD, is included in (c)MM/SM1 cancers. Based on these facts, (c)MM/SM1 cancers are considered as an indication for ESD.

Lateral extent of cancer

Although ESD is an effective treatment, extensive esophageal endoscopic resection can lead to postoperative esophageal strictures, with rates of postoperative stricture after non-circumferential and whole circumferential resection of 60.7%-75% and 100%, respectively, if preventive measures are not applied^[19-21]. Stricture after esophageal ESD causes dysphagia and requires multiple, long-term endoscopic balloon dilatations. It thus has a negative impact on the patient's quality of life and may delay additional chemoradiotherapy after non-curative resection. However, the use of appropriate preventive measures can reduce the proportion of strictures after non-circumferential resection to 11.3%-36.2%^[19,20,22]. Non-circumferential lesions are thus considered as an indication for ESD, whereas the risk of stricture following circumferential resection remains high, despite preventive measures.

The application of stenosis-preventive measures following circumferential resection was associated with stenosis rates of 76% in 45 patients who received steroid injection therapy^[23-27], 55% in 44 patients who received oral steroid therapy^[25,26,28-30], and 71% in 14 patients who received both injected and oral steroid therapy^[19]. However, these studies included widespread lesions with a mean major axis length of 6 cm. A previous report^[26] showed that a resection diameter > 50 mm increased the stricture risk: when the major resection axis length was > 50 mm, 85% of patients (11/13 patients) required at least six sessions of dilatations, compared with only 17% of patients (1/6 patients) with a length ≤ 50 mm. Furthermore, the administration of oral steroid prednisolone at a starting dose of 30 mg and tapered for 12-18 weeks limited the stenosis rate to 27.3% (3/11 patients) in patients who underwent whole-circumferential resection, requiring a mean of only 1.6 sessions of balloon dilatation^[25]. These reports confirm that stricture relief can be achieved more easily in tumors with a major axis length ≤ 50 mm, and effective methods are being developed to prevent stricture following whole-circumferential stenosis.

Expected curability is another important factor determining the indication for ESD. Although, no studies have reported on the pathologic results for cEP/LPM cancer with circumferential extent, a previous report showed that approximately 70% of cEP/LPM cancers ≥ 50 mm were (p)EP/LPM cancers^[31]. Conversely, however, another study^[32] showed that only 14% (2/14 lesions) of (c)MM/SM1 whole-circumferential cancers were (p)EP/LPM cancers. In addition, 86% (12/14 lesions) of (c)MM/SM1 whole-circumferential cancers were at high risk of metastasis (submucosal cancer or vascular invasion positive) or had lymph node metastasis. From the perspective of accuracy for preoperative diagnosis of cancer invasion depth, further investigation is needed regarding the adequacy of ESD for (c)MM/SM1 whole-circumferential cancers. Considering the expectancy of curability and postoperative complications, ESD is therefore recommended for cT1a-EP/LPM superficial SCCs with a major axis length ≤ 50 mm and involving the entire circumference of the esophagus, upon implementing preventive measures for stenosis.

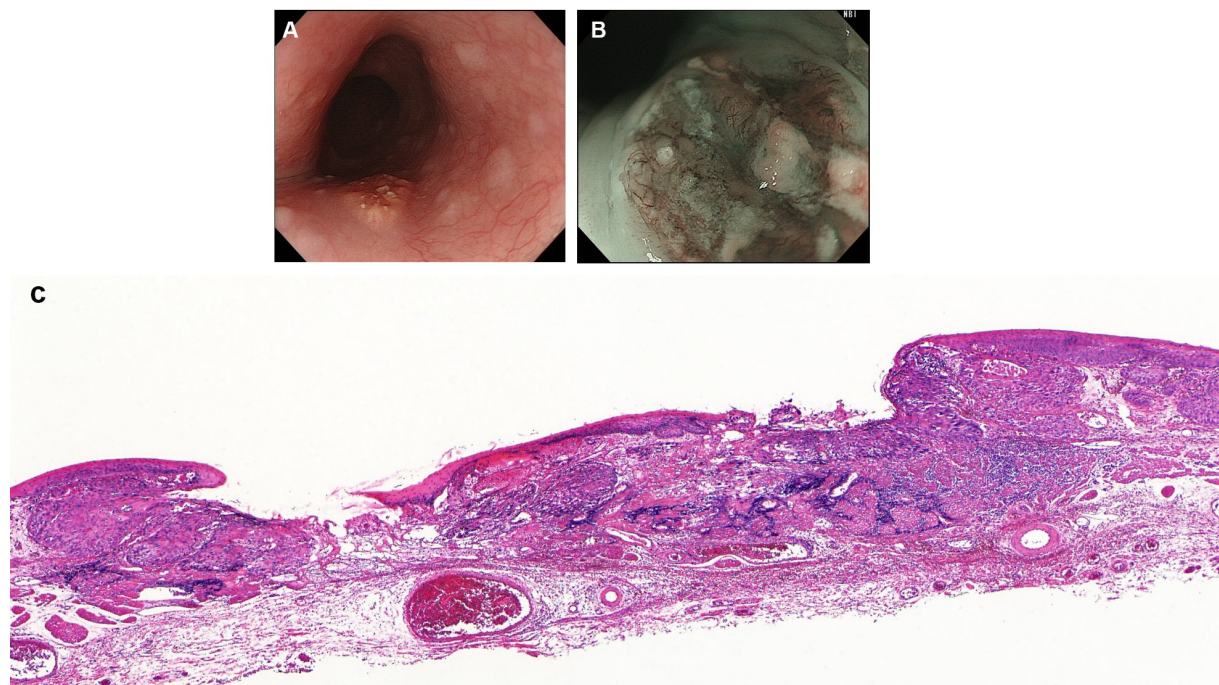


Figure 2. Clinical T1a-muscularis mucosae/T1b-submucosa 1 (MM/SM1) cancer finally diagnosed as pathological lamina propria cancer by pathological examination of resected specimen. (A) Lesion was slightly elevated on white light imaging. (B) Lesion was mainly occupied by B2 vessels. (C) Pathological diagnosis of resected specimen in our facility was cancer invading lamina propria without vascular invasion (hematoxylin and eosin staining).

Diagnosis of metastasis

To determine treatment strategy for T1 esophageal SCC, clinical stage of the cancer should be confirmed by such means as computed tomography of the neck, chest, and abdomen, and positron-emission tomography. Although ESD is indicated to patients with T1N0M0, accuracy of clinical diagnosis for N0M0 is not yet elucidated. A previous study showed that the accuracy of clinical N0 for T1b cancer was 73%^[33]. In other words, despite a clinical diagnosis of N0, there still exists a risk of metastasis. We therefore have to conduct strict curability assessment after ESD and apply additional treatment to patients with high risk for metastasis even when the cancer is clinical N0.

CURABILITY ASSESSMENT [Table 2]

Curability following ESD is determined based on the histological findings of the resected specimens. Horizontal and vertical margin statuses correlate well with the risk of local recurrence, while cancer invasion depth and vascular invasion statuses correlate well with the risk of metastasis. For the assessment of vascular invasion, additional assessment using immunostaining need to be considered because it may enhance the detection of vascular invasion^[34].

Horizontal and vertical margin status

The resection can be judged as curative in terms of margin status if both the horizontal and vertical margins are negative. If the horizontal margin is positive, careful surveillance is recommended because of the risk of local recurrence, and if the vertical margin is positive, additional treatment, such as esophagectomy or chemoradiotherapy, is recommended to eradicate the residual cancer.

Table 2. Curative ability assessment of endoscopic submucosal dissection based on cancer invasion depth and vascular invasion status

<u>Curative resection</u>
√ Pathological T1a-epithelial/lamina propria without vascular invasion
<u>Non-curative resection and undetermined recommendation for additional treatment</u>
√ Pathological T1a MM without vascular invasion
<u>Non-curative resection and additional treatment recommended</u>
√ Pathological T1b cancer invading the submucosa
√ Pathological vascular invasion-positive

MM: Muscularis mucosae.

Cancer invasion depth and vascular invasion

(p)EP/LPM cancer

Although metastasis may develop in (p)EP/LPM cancers without vascular invasion, the risk of the metastasis is as low as 0.4%^[35]. The resection is judged as curative if the histological findings of the resected specimen show (p)EP/LPM cancer without vascular invasion and if the horizontal and vertical margins are negative. Other cancers, (p)MM, (p)SM, or tumors with vascular invasion are considered as non-curable in terms of cancer invasion depth and vascular invasion.

(p)MM cancer

The ESD/EMR Guidelines for Esophageal Cancer^[13] analyzed the incidences of metastasis of (p)MM cancers in surgically and endoscopically resected patients. For (p)MM cancer without vascular invasion, the lymph node metastasis rate was 4/38 (10.5%) in surgically resected patients^[36], compared with 12/216 (5.6%) in the follow-up observation group after endoscopic resection^[13]. Given the considerable risk of metastasis, pathologically diagnosed (p)MM cancer without vascular invasion is judged as non-curable. However, considering the reduced quality of life and the possibility of treatment-related death associated with additional surgical resection, as well as delayed adverse events and treatment-related deaths following additional chemoradiotherapy, these treatments are not conducted in most cases. In addition, patients are usually informed that metastasis can occur at certain rates and that it is crucial to perform careful follow-up, including screening for metastasis.

Regarding (p)MM cancer with vascular invasion, the lymph node metastasis rate was 5/12 (41.7%) in surgically resected patients^[36] compared with 3/14 patients (21.4%) in the follow-up observation group after endoscopic resection^[13]. Given the high risk of metastasis, pathologically diagnosed (p)MM cancer with vascular invasion is thus considered to be non-curable, but additional treatment with surgical resection or chemoradiotherapy is recommended for these patients.

(p)SM cancer

The ESD/EMR Guidelines for Esophageal Cancer analyzed the incidences of metastasis of (p)SM cancers in surgically and endoscopically resected patients. Analyses of resected specimens from patients with (p)SM1/SM2 esophageal SCC who received surgical resection as first-line treatment, including patients with vascular invasion, showed concurrent lymph node metastasis in 43/170 patients (25.3%) with (p)SM1 cancers and 49/196 patients (25%) with (p)SM2 cancers, compared with 8/43 patients (18.6%) with (p)SM1 cancers and 3/20 patients (15%) with (p)SM2 cancers in the follow-up observation group of patients who received endoscopic resection as first-line treatment, including patients with vascular invasion. In addition, recent retrospective study showed that lymphatic invasion and (p)SM2 were independent risk factors for metastatic recurrence^[37]. Given the high proportion of metastasis, a histological finding of (p)SM cancer is judged as non-curable, and additional treatment with surgical resection or chemoradiotherapy is

recommended for these patients.

FUTURE PERSPECTIVES

Widespread use of ESD

ESD has higher en bloc resection rate and R0 resection rate than EMR. However, piecemeal EMR is still conducted in some areas. Widespread use of ESD is desired by overcoming its technical difficulties.

Best treatment for circumferential lesions

ESD is a minimally invasive treatment with high curative potential in patients with esophageal cancer. However, circumferential endoscopic resection can result in intractable stenosis, considerably reducing the patient's quality of life. Chemoradiotherapy is another option for circumferential lesions. A literature search failed to find any previous studies that described the specific survival rates of patients with circumferential lesions. Survival analyses and comparative studies of ESD and chemoradiotherapy for circumferential lesions are therefore required to determine the best treatment for circumferential lesions.

Curability assessment for (p)MM cancer

Assessing the curability of (p)MM cancer without vascular invasion is an issue in clinical practice. Previous studies examining the incidence of metastasis following endoscopic resection were conducted retrospectively, did not make it clear if the pathological evaluations were performed using immunostaining, and lacked thorough and long-term follow-up observations. Future prospective studies are anticipated to evaluate the metastasis rates in patients with (p)MM cancer based on detailed histological evaluations and intensive follow-up.

Indication of additional treatment after ESD

The indications for additional treatment are mainly determined based on the risk of metastasis and the patient's condition. Considering our aging society, additional treatment may not be indicated even in patients with a substantial risk of metastasis. However, detailed stratification of metastasis risk based on histologic findings is currently not possible, and further studies are needed to develop factors to determine detailed individual risks of metastasis.

Conclusion

An accurate preoperative diagnosis, appropriate indication, and adequate curability assessment based on the pathological diagnosis of resected specimens are important for effective ESD.

DECLARATIONS

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Authors' contributions

The author contributed solely to the article.

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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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Retroperitoneal approach for robot-assisted partial nephrectomy: a step-by-step description of surgical technique

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Abstract

In the last decades, minimally invasive partial nephrectomy (PN) has gained traction and, as of today, robot-assisted laparoscopic PN (RAPN) is increasingly being performed; this procedure might be performed with a transperitoneal or retroperitoneal (rRAPN) approach. However, rRAPN is less standardized in the literature. Therefore, we describe our rRAPN technique using a da Vinci Xi Surgical System and four robotic arms. First, with the patient placed in full flank position, the camera port is placed at the level of the Petit's triangle apex. Retroperitoneal space is created by turning the index finger in a 180° movement through this port. After, the two first 8 mm robotic ports are blindly placed with the surgeon's index finger guide, 8 cm far from the first port, respectively along the anterior and posterior axillary line; 3-5 cm caudally to the last one, a 12 mm AirSeal® assistant port is placed in the same manner. To create space for the last 8 mm robotic port, the peritoneum is reflected medially and downward off of the transversus abdominis muscle laparoscopically. Only then, the last port is placed under direct vision 8 cm ventral and about 2 cm cephalad from the port on the anterior axillary line. The robotic ports placement will result in a caudally convex arc. This technique, due to the extensive use of the surgeon index, implies fast access to the retroperitoneum, protects the underlying anatomical structures from damage, and, due to the trocar positioning along an arc, lowers the arm conflict risk.



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Keywords: Renal cancer, robotic partial nephrectomy, nephron sparing surgery, retroperitoneal access

INTRODUCTION

Open partial nephrectomy (PN) has long been the gold standard for treatment of renal masses amenable to nephron-sparing surgery. However, in the last decades, minimally invasive approaches have gained traction in this field, due to improved postoperative recovery without compromised functional, perioperative, and oncological outcomes^[1].

Minimally invasive PN may be performed either with laparoscopy (LPN) or with robot-assisted laparoscopy (RAPN); due to the highly advanced laparoscopic skills needed for LPN, RAPN is increasingly being performed, with reports in the literature of shorter warm ischemia time, length of stay, blood loss, and superior functional and oncological outcomes with the latter^[2,3].

As with standard laparoscopic techniques, RAPN might be performed with either transperitoneal (tRAPN)^[4] or retroperitoneal (rRAPN) approach^[5,6].

No specific indication of in which candidates tRAPN or rRAPN should be used can be found in current guidelines, and in the literature the two approaches have been shown to offer equivalent perioperative morbidity, functional and pathological outcomes regardless of tumor location^[7,8]. However, the choice of surgical approach is influenced by tumor location: tRAPN for medial and anterior masses and rRAPN for posterior ones.

The three- and four-arm RAPN techniques are well described in the literature^[9-12]. However, a retroperitoneal robotic access technique is less standardised. Therefore, we describe our rRAPN access technique step-by-step, showing all relevant details in the available video [[Supplementary Video 1](#)], focusing on patient positioning, port placement, generating retroperitoneal space, and robot docking.

METHODS

Patient preparation

For retroperitoneal approaches, bowel preparation is not administered and fasting is indicated from midnight. A type and screen is sent, and two packs of red blood cells are available in the operating room, as for all renal surgeries performed in our department.

Patient positioning

After general anesthesia is established, the patient is positioned in a full flank position with the ipsilateral side up relative to the renal tumor and the arms extended on supports to facilitate retroperitoneal access. The bed is bent to widen maximally the distance between the iliac crest and the ribs and, eventually, flipped to the anti-Trendelenburg position, in the case of a particularly prominent iliac crest (typically in women) [[Figure 1](#)].

Next, after disinfection, surgical drapes are positioned along the paravertebral line laterally and the parasternal line medially, just under the basisternal line cranially and the bisiliac line caudally, in order to provide full access to the retroperitoneal space, as well as exposure of the whole abdomen in case of need to convert to a transperitoneal approach.

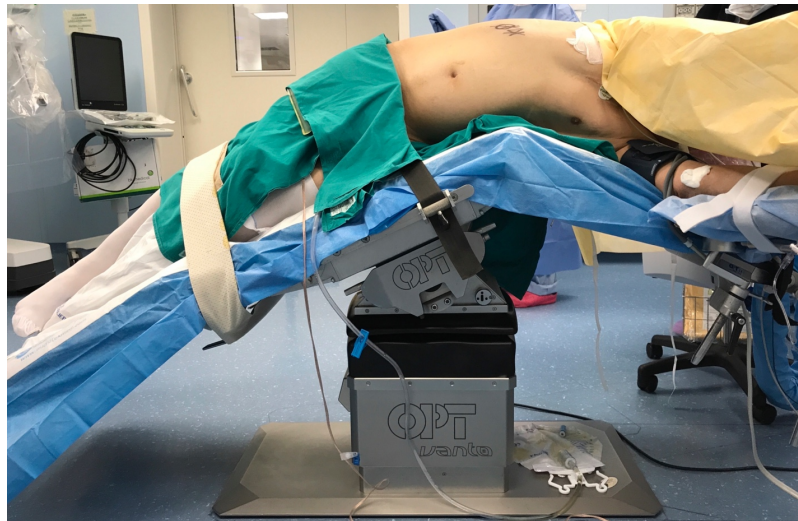


Figure 1. Full flank position and bent bed to increase the distance between the iliac crest and the ribs.

Access

To identify placement of the camera port and creation of the retroperitoneal space, the iliac crest, 12th rib, and the inferior lumbar (Petit's) triangle are important landmarks and can be marked out [Figure 2A]. A 1.5 cm vertical incision is made at the level of the apex of the Petit's triangle. Subcutaneous tissue is divided with cautery until the internal oblique muscle is reached. Thereafter, the muscle fibers of the internal oblique muscle are bluntly finger-separated, and then Metzenbaum scissors are used to penetrate the thoracolumbar and transversalis fasciae and enter the retroperitoneal space [Figure 2B].

Retroperitoneal space creation and port placement

After inserting the index finger into the previous incision, the retroperitoneal space between the posterior layer of renal fascia and the transversalis fascia is created by turning the index finger in a 180° movement, running it as close as possible to the abdominal wall, separating the pararenal fat and peritoneum from the transversalis fascia [Figure 3]. During this maneuver, the sensation of the finger running on a smooth surface (the transversalis fascia) and the palpation of the internal surface of the 12th rib and the body of the psoas muscle are crucial to ensure that the surgeon is developing the right space. In case these internal and haptic landmarks are not perceived, the finger could be in the wrong place, such as in between the muscles or inside the peritoneal cavity.

Then, the first two 8 mm robotic ports are placed at a distance of 8 cm from the first access port - it generally corresponds to one-finger length - one along the anterior axillary line, the other along the posterior axillary line, 1-2 cm cranially to the level of the camera port. A 12 mm AirSeal® assistant port is placed on the posterior axillary line, 3-5 cm caudally to the 8 mm robotic port [Figure 2C-E]. These first three trocars are bluntly positioned in a "blind fashion", keeping the index finger through the first access port inside the retroperitoneal space, pushing on the abdominal wall at the site of trocar insertions. In this way, the positioning is both fast and safe, although blind, because the internal finger guarantees that nothing else than the abdominal wall is along the route of the trocar. After the insertion of the two first 8 mm robotic trocars and the AirSeal® trocar, the 8 mm robotic camera port, through a Hasson cone, is placed in the first incision. Then, pneumoretroperitoneum is created at 12 mmHg of carbon dioxide and the 0° robotic camera can be inserted in the retroperitoneal cavity.

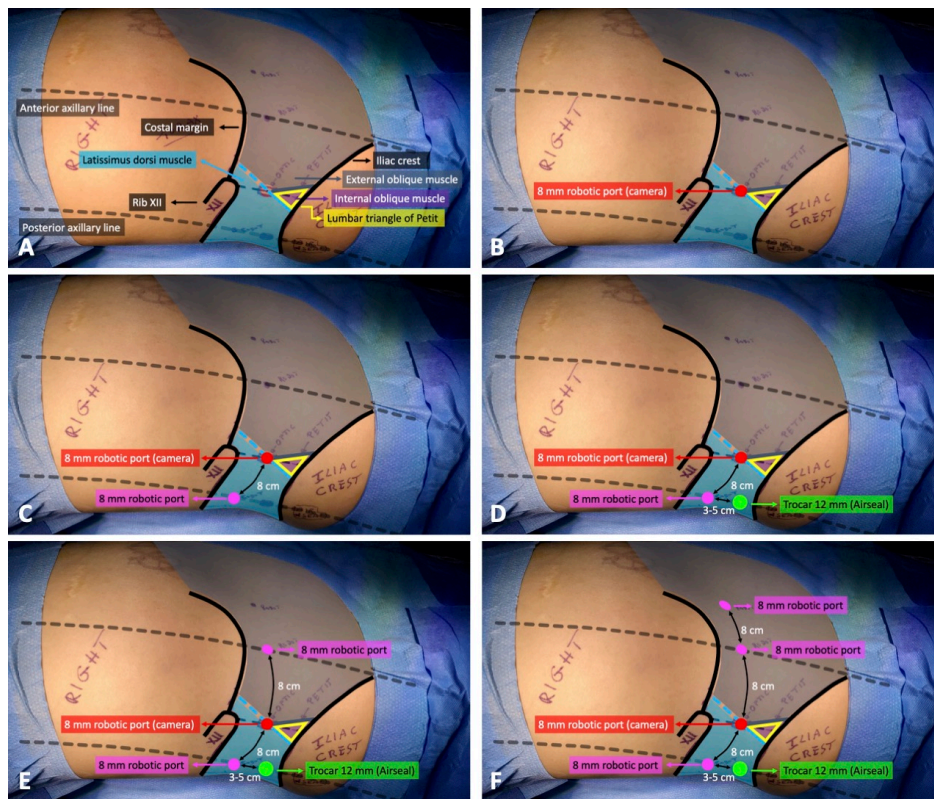


Figure 2. Port placement sequence. (A) The iliac crest, 12th rib, and inferior lumbar (Petit's) triangle are marked. (B) A 1.5 cm vertical incision is made at the level of the apex of the Petit's triangle for the 8 mm robotic camera port. (C) Finger-guided 8 mm robotic port placement along the posterior axillary line. (D) Finger-guided 12 mm AirSeal assistant port placement along the posterior axillary line. (E) Finger-guided 8 mm robotic port placement along the anterior axillary line. (F) Under vision, 8 mm robotic port placement 8 cm ventrally to the anterior axillary line.

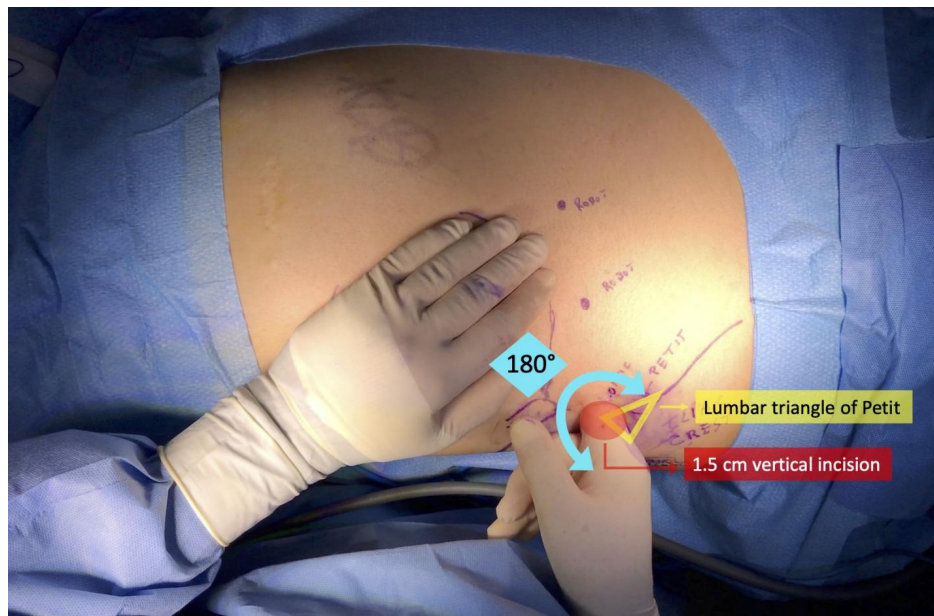


Figure 3. Retroperitoneal space creation: 180° index finger movement, inserted into the incision at the level of the apex of the Petit's triangle, to separate the perirenal fat and peritoneum from the transversalis fascia.

Thereafter, blunt laparoscopic instruments, placed into the AirSeal® assistant port and the 8 mm robotic port in the posterior axillary line, are used to gently reflect the peritoneum medially and downward from the transversus abdominis muscle and allow the creation of space anteriorly for the fourth 8 mm robotic port [Figure 4].

This is placed under direct vision along the other robotic ports arc, 8 cm ventral and about 2 cm cephalad from the one placed on the anterior axillary line [Figures 2F]. A needle can be inserted to confirm the site before the port is inserted under vision.

Particular care should be taken during this critical step to avoid breaching the peritoneum. If this does happen, surgery may still proceed aided by using a 4th robotic arm by retracting anteriorly the kidney and plugging the opening; alternatively, the breaching can be widely opened and surgery converted to a posteriorly-approached transperitoneal procedure.

The final aspect of the robotic ports placement will result in a caudally convex arc, which creates generous movement space for the four robotic arms (the camera port and the three robotic arms), as well as for the bedside assistant surgeon [Figures 5-7].

Robot docking

Using the da Vinci Xi Surgical System with a rotating boom, the robot can be brought in at several different locations and the tower rotated to align with the trocars. In our practice, the patient cart is brought in from the patient ventral side, the boom is extended, the camera is docked, the target surgical site is confirmed, the Xi system automatically calibrates the arms, and then we dock them. Once docked, the robotic instruments are inserted under direct vision starting from the fourth arm to facilitate the vision: Maryland bipolar forceps in the left hand, monopolar curved scissors in the right hand, and large needle driver in the fourth arm. The assistant access to the kidney is through the 12 mm Airseal® assistant port [Figure 8].

Surgical technique

The first step consists in dissecting the pararenal fat to expose the psoas muscle and the posterior layer of renal fascia [Figure 9A]. The next step is to make an incision in the posterior layer of renal fascia just above and parallel to the psoas muscle, exposing the perirenal fat [Figure 9B and C]. At this point, perirenal fat is dissected from the kidney following the plane along the psoas muscle, which is exposed by retracting anteriorly the kidney using the 4th arm [Figure 9D]. When a perirenal fat pulsation is found, the renal vascular hilum can be easily identified [Figure 9E and F], thus the rest of the operation follows the standard tRAPN steps. At the end, the specimen is retrieved through the camera port.

DISCUSSION

Since the first laparoscopic nephrectomy by Clayman *et al.*^[13] in 1991 and a few years after the retroperitoneal approach by Gaur *et al.*^[14] were described, a debate about the different minimally invasive PN approaches was started, and it is still going on as of today.

Selection of the optimal approach plays a critical role in renal surgery. This must be guided by several aspects including the surgeon's experience, the characteristic and location of the kidney mass, and the patient's characteristics and clinical history. Due to larger intra-abdominal space and familiar anatomical landmarks, the transperitoneal access may especially be attractive at the start of the surgeon's experience in this field. On the other hand, a smaller working space and the absence of anatomic landmarks, which limit retroperitoneal approaches, may disorient the beginner surgeon^[15]. In addition, limited working space

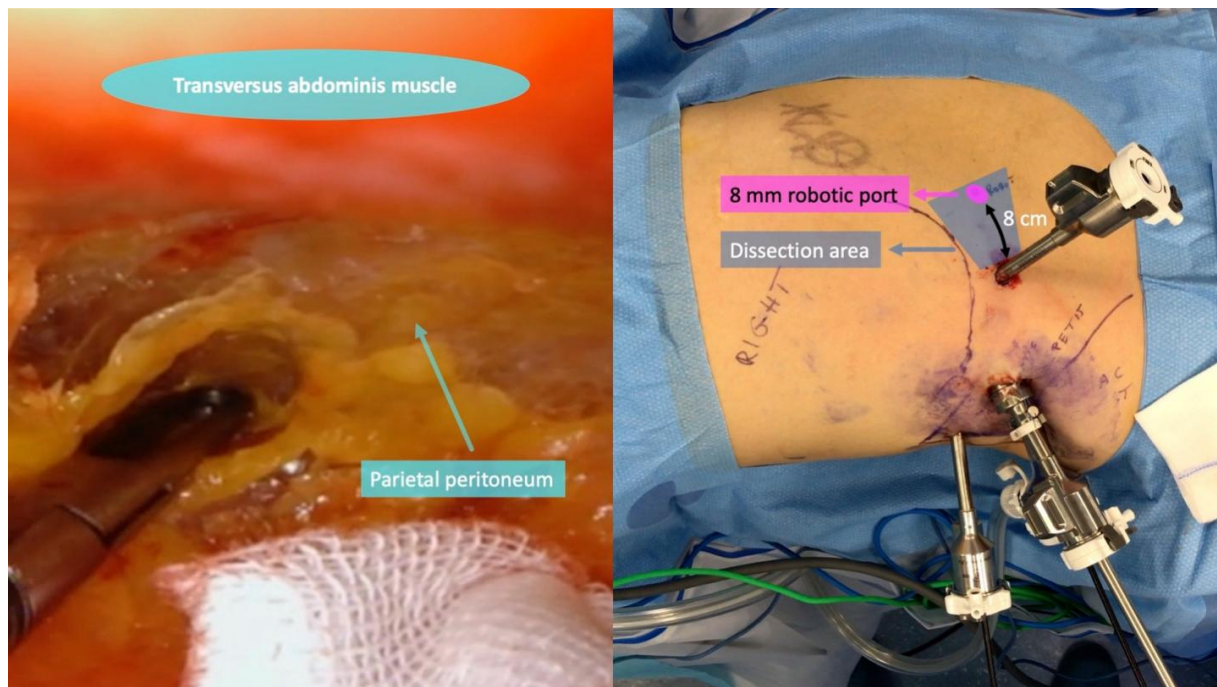


Figure 4. Ventral laparoscopic blunt dissection of the perirenal fat and peritoneum to create space for the fourth port.

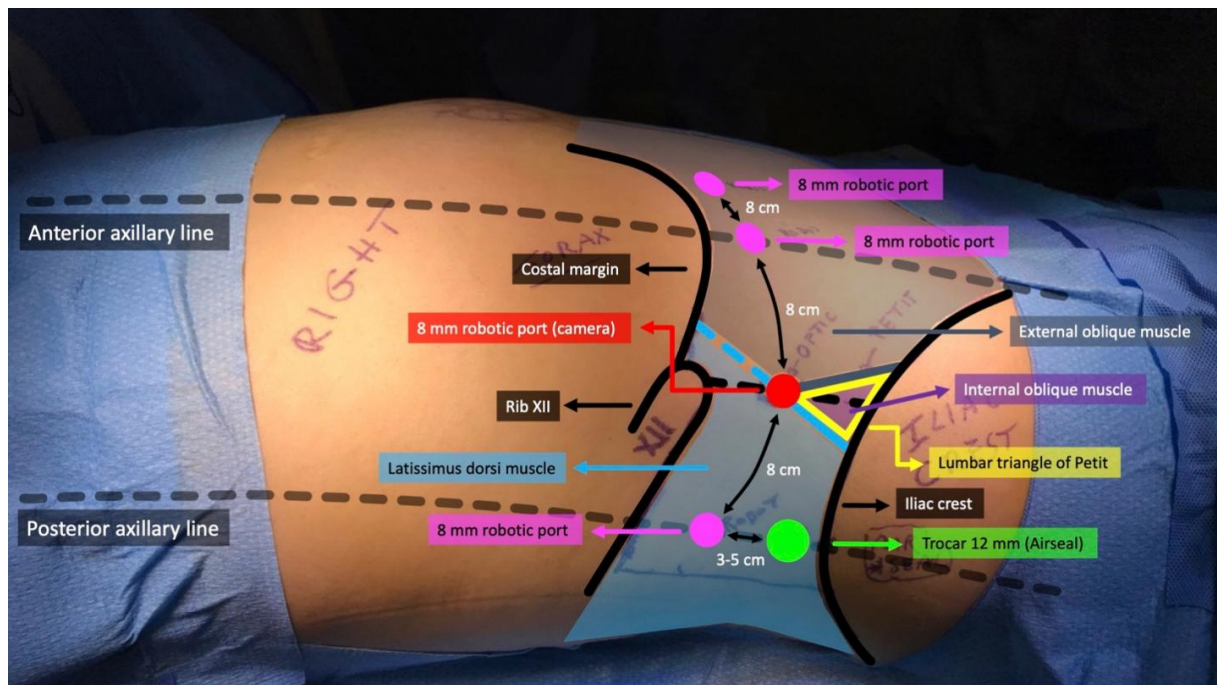


Figure 5. Port configuration for retroperitoneal robot-assisted partial nephrectomy (full lateral view).

reduces triangulation and freedom of movement and increases instrument clashing, making it difficult to use a 4th robotic arm^[16].

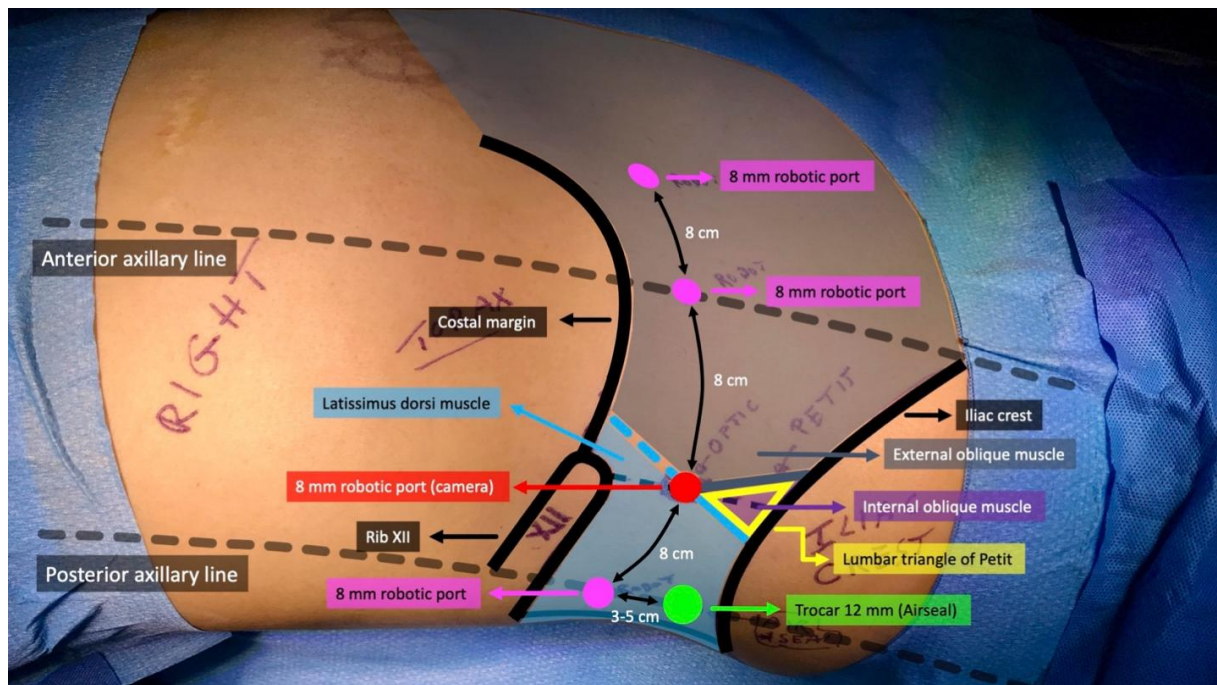


Figure 6. Port configuration for retroperitoneal robot-assisted partial nephrectomy (antero-lateral view).

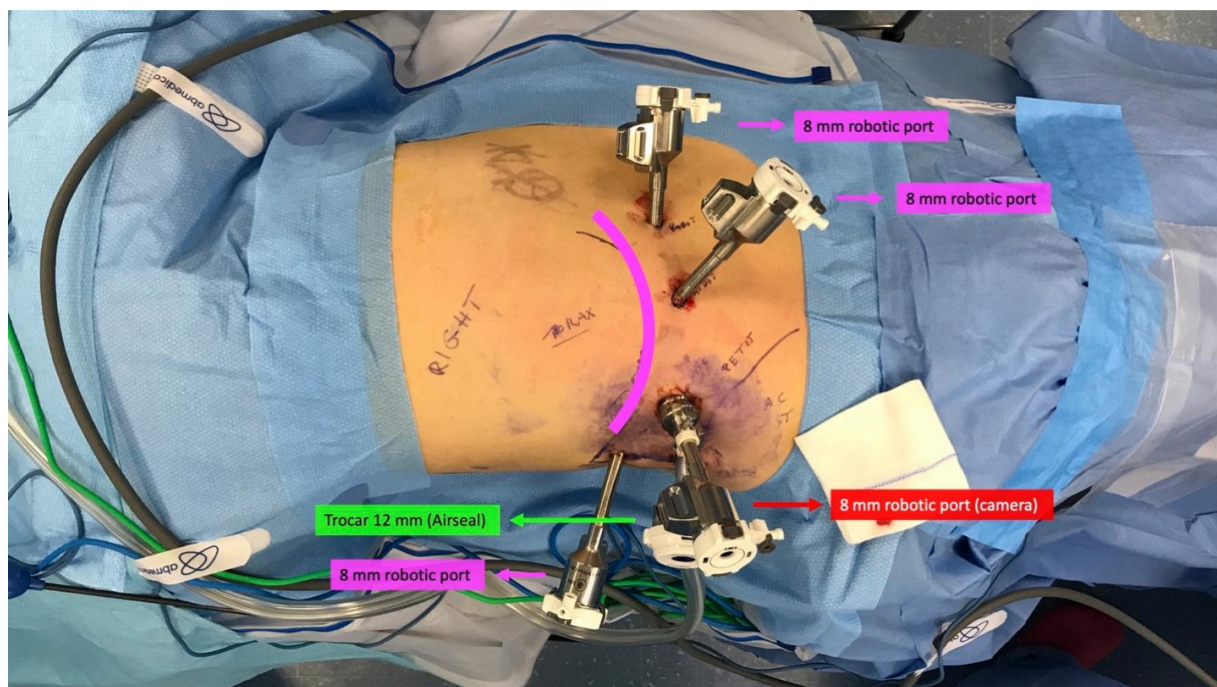


Figure 7. Final port placement delineates a caudally convex arc.

Since it was first described by Patel *et al.*^[5] in 2009, rRAPN has provided a quick and direct access to the renal artery, encountered before the renal vein, without the need for colon mobilization, thus reducing the risk of ileus and with the advantage of faster recovery of postoperative bowel function^[16-19]. A further potential benefit is that the retroperitoneal space may tamponade hemorrhage and prevent peritonitis



Figure 8. Docked da Vinci Xi Surgical System patient cart, previously positioned ventral to the patient.

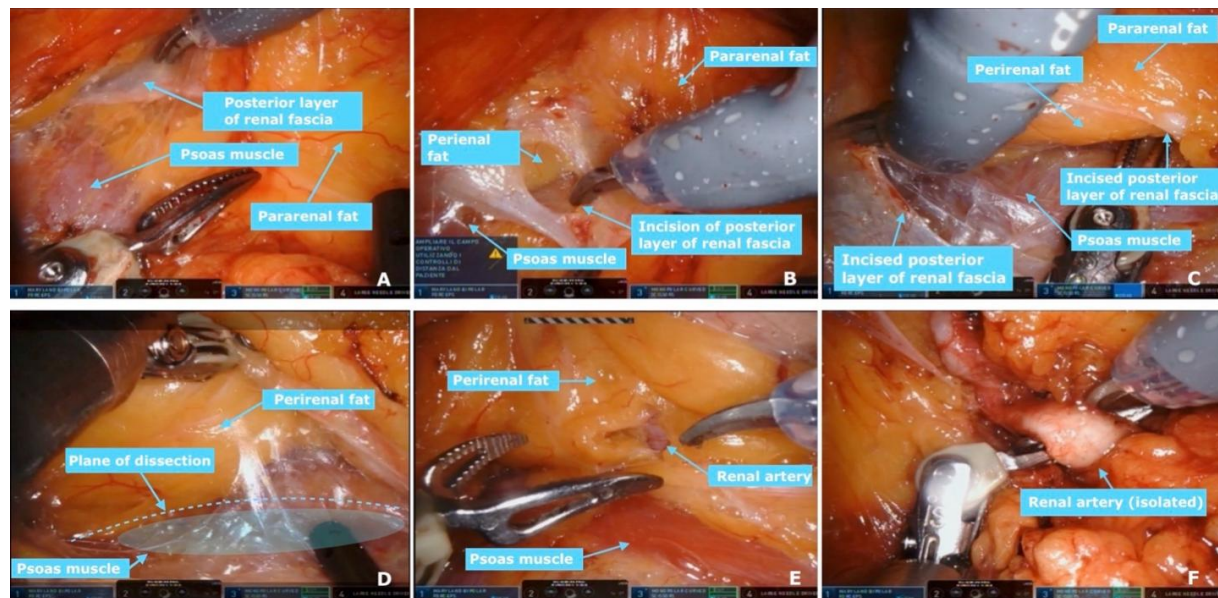


Figure 9. Surgical technique for retroperitoneal robot-assisted partial nephrectomy: (A) dissection of the pararenal fat to expose the psoas muscle and the posterior layer of renal fascia; (B, C) incision in the posterior layer of renal fascia just above and parallel to the psoas muscle, exposing the perirenal fat; (D) dissection of the perirenal fat from the kidney following the plane along the psoas muscle; and (E, F) isolation of the renal artery from the perirenal fat.

caused by urinary fistulas^[16].

The significance of tumor location on treatment choice is supported by the categorization of anterior and posterior location by both the RENAL and PADUA scores^[20,21]. rRAPN is ideally suited for posterior or lateral renal masses, especially in the middle and upper pole of the kidney, because it allows direct access to the posterior and lateral surface of the kidney and minimizes the extent of dissection inside renal fascia, but it can be applied to anterior and medial masses in patients with a history of extensive previous abdominal surgery and/or any pathological condition that may increase the risk of intra-abdominal scarring and adhesions (e.g., previous peritoneal pathology or peritonitis and peritoneal dialysis)^[16] bearing in mind that, as stated above, rRAPN represents only an alternative approach for posterior renal masses. Thus, the surgeon's experience and not the tumor location cover a primary role during selection of the optimal surgical approach for posterior masses^[7,8].

Previous history of retroperitoneal surgery or percutaneous procedures represents a relative contraindication to rRAPN, as well as highly complex tumors and anatomical variations (e.g., horseshoe kidney and pelvic kidney). Extremely obese patients are more difficult to treat retroperitoneally due to the high volume of adherent perirenal fat and a transperitoneal approach should be preferred^[15,16].

Our retroperitoneal space creation technique, due to the extensive use of the surgeon index to guide the procedure, implies fast access to the retroperitoneum. Moreover, the tactile feedback from the surgeon index provides insight on the tissues' characteristics, rendering the blunt dissection of the pararenal fat from the trasversalis fascia almost atraumatic. The trocars' placement with digital protection and feedback is safe and protects the underlying anatomical structures from the trocars' damage, while enabling fast placement. In the literature, retroperitoneal space creation is almost always described using a balloon dissector. The absence of a trocar balloon dilator further reduces the operative time and cost. Meanwhile, placing the

robotic ports in a caudally convex arc, 8 cm apart, lowers the risk of arm conflict. This robotic port configuration was already described by Mittakanti *et al.*^[22] reporting the rRAPN technique using the da Vinci Xi Surgical System. Conversely, placing the assistant port dorsally and not ventrally enables always having two instruments ventral (the two 8 mm robotic ports) and two instruments dorsal (the other 8 mm robotic port and the 12 mm AirSeal® assistant port) to the camera. This balances retroperitoneal space management and provides, without triangulation, improved freedom of movement for the robotic arms, with two instruments coming from each side, as opposed to other described techniques, where three instruments are brought in anteriorly (two 8 mm robotic ports and the assistant port), reducing potential clashing of the robotic arms. This is further aided by the da Vinci Xi laser targeting system and automatic arm calibration. In addition, this port configuration gives the assistant more room to work externally and provides an improved angle at which to provide assistance.

Furthermore, the advent of the most recent surgical robot, the single-port da Vinci SP, may facilitate an even more flexible access, even in the field of retroperitoneal renal surgery^[23].

Conclusions

We present in this manuscript a new retroperitoneal access technique for RAPN, developed to facilitate the robotic approach for posterior masses, without any need of a balloon dissector and with better retroperitoneal space management. However, data regarding this technique are still maturing, therefore further studies will be presented in time.

DECLARATIONS

Authors' contribution

Study concept and design: Antonelli A, Tafuri A, Bianchi A

Drafting of the manuscript: Bianchi A, Cianflone F

Critical revision of the manuscript for important intellectual content: Antonelli A, Cerruto MA, Migliorini F

Supervision: Antonelli 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

All images were obtained from the same patient who signed an informed consent.

Consent for publication

Not applicable.

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Editorial

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What role does hand-assistance have in minimally invasive pancreatic surgery?

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MINIMALLY INVASIVE SURGERY: RATIONALE, ADVANTAGES AND LIMITATIONS

Surgery poses an important stress on the patient from both physical and psychological points of view *per se*. It has become clearer with time that, regardless of the type of surgical operation, a smaller surgical incision could reduce the operation-induced stress. With advancements in technology, great efforts have been made in trying to reduce this burden on the patient, leading to the development of minimally invasive surgery (MIS)^[1,2]. MIS has gained increasing support since its introduction and has undergone continuous improvements and evolutions to the point of becoming, nowadays, the standard of care for many surgical procedures such as cholecystectomy, adrenalectomy, splenectomy, and fundoplication. MIS encompasses several different approaches which have in common the aim of decreasing the impact of the surgical operation on the patient. The first approach to be developed and widely accepted in clinical practice was laparoscopy. Among the well-established advantages of laparoscopic surgery, we have decreased pain, shorter length of stay, faster postoperative recovery, and a better visualization of secluded anatomical spaces which would otherwise require a large incision to be correctly exposed^[3]. All of this comes at the price of decreased dexterity, diminished tactile feedback, and inherent limitations posed by restricted degrees of freedom of laparoscopic instrumentation, which may result in a longer operative time compared to the open approach for complex surgical procedures^[4]. In recent years, an alternative to the laparoscopic technique has been proposed with the introduction of robotic platforms in surgery. Potential advantages of robotic surgery are filtration of tremors, better dexterity, higher degrees of freedom with the EndoWrist system, and better



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operative field visualization with 3D imaging. Nonetheless these advantages have to be balanced with drawbacks such as lack of haptics and high cost in terms of both initial investment in purchasing the robotic platform and single operation cost.

MIS IN THE PANCREATIC SURGERY FIELD: A STEEP PATH

Despite all the hype around these new technologies, the implementation and diffusion of MIS have been hampered by the large amount of time and dedication necessary to master the techniques to have results comparable to the open approach. The concept of learning curve became particularly popular with the advent of minimally invasive surgery, when surgeons needed to completely rethink their abilities and adapt them to new techniques and technologies. It has also been postulated that the learning curve appears to be longer in MIS relative to open surgery, and that the curve becomes steeper and steeper with the increasing complexity of surgical procedures^[5]. For complex major abdominal surgeries, a great number of procedures is required to master the technique, and there may be dangerously high morbidity and mortality rates at the beginning of the learning curve. This has been particularly the case of pancreatic surgery.

Despite the appeal of MIS and its widespread adoption in several fields of surgery, the attitude of pancreatic surgeons has been initially tepid. On the one hand, there was the conceptual problem of whether in complex and demanding surgical operations such as pancreatic resections the size of the incision can truly be considered the main contributor to surgical trauma. On the other hand, some peculiar aspects of pancreatic surgery have initially hampered the widespread diffusion of the minimally invasive approach in this field: the peculiar retroperitoneal location of the pancreas, its delicate texture and proximity to major vessels, the complexity of the dissection, the concerns regarding oncological safety in the case of malignancy, the difficulty of the anastomotic components, and the still relatively high morbidity and mortality that characterize pancreatic resections^[6-10]. Another more practical matter is the relative rarity of pancreatic diseases and the complexity of most cases, which make them not suitable to be approached minimally invasively by surgeons at the beginning of their learning curve; the result is an even longer time to reach proficiency and an acceptable morbidity and mortality rate^[11].

Reports of the initial experience with totally laparoscopic pancreatic surgery showed no apparent advantage for pancreaticoduodenectomy, with no improvement in postoperative outcomes and increased morbidity. Conversely, the results are promising for distal pancreatectomy, since it was associated with acceptable operative time and reduced morbidity and length of stay (LOS)^[12].

HAND-ASSISTED LAPAROSCOPIC SURGERY

Rationale and limitations

To overcome the difficulties in adaptation of complex procedures from an open approach, some hybrid techniques have been developed for laparoscopy.

One of the proposed approaches is hand-assisted laparoscopic surgery (HALS): a mini-laparotomy is planned through which the surgeon can insert his or her hand covered by a glove or a hand port that prevents the loss of the pneumoperitoneum. This allows for the surgical operation to be performed via laparoscopy but with the help of an intra-abdominal hand. At the beginning, this technique was greeted with skepticism because of the need to perform a laparotomic incision, which is in direct contrast with the principle of minimal invasivity and because of the lack of adequate instruments able to maintain the pneumoperitoneum with an intra-abdominally inserted hand^[13]. However, with the development of appropriate instruments, HALS found its niche in enabling the surgeon to start approaching major abdominal operations in laparoscopy, with as safety net the familiarity and the expertise of having a hand

directly in contact with the structures. Clear pros of this approach are restoration of the tactile feedback and better manipulation of tissues, such as better organ retraction, finger blunt dissection, exposure and control of possible unexpected intraoperative bleeding and complications^[14,15], and a shorter operative time than laparoscopy^[16], while maintaining some of the advantages of MIS over the open approach, notably a lower estimated blood loss and a shorter LOS. Among the cons, there is clearly the additional surgical trauma posed by the mini-laparotomy, although this problem may be partially mitigated by using this technique in operations which would already require an incision to retrieve the resected specimen. Moreover, despite the handiness of having a direct access to the abdominal cavity, the presence of the hand may reduce the space and range of movements of laparoscopic instrumentation and impair vision^[13].

Fields of use

After its introduction, this technique was initially adopted in several different fields of surgery, in which a pure laparoscopic approach was still striving to be undertaken. In esophagogastric surgery, HALS was applied to both trans-hiatal esophagectomy and total and partial gastrectomy with good results in terms of postoperative and oncological outcomes^[17-19]. A trial was also made in bariatric surgery, but no advantages were found over the open approach for gastric bypass in terms of incidence of incisional hernia and reduction of LOS despite an increased cost^[20]. One of the areas in which HALS has had greater success is colorectal surgery in which an incision is needed anyway, no matter the approach, to extract the specimen and possibly perform the anastomosis. HALS has been used for partial or total colectomy, anterior rectum resection, and abdominoperineal resection, and it maintains the advantages of laparoscopy in terms of bowel movements, refeeding, and hospital stay^[21-24]. Another application of HALS was in the living-donor nephrectomy, where it showed a shorter warm ischemic time than pure laparoscopy, while offering a smaller incision and faster recovery than the open approach^[25-28]. From initial reports, HALS appeared to facilitate the laparoscopic approach, increasing the level of subjective safety and thus shortening the learning curve.

HALS in the pancreatic surgery field

In pancreatic surgery, preliminary data were presented by Cuschieri^[29] and Gagner and Gentileschi^[30], in the early era of pancreatic laparoscopy, presenting the advantages of the hand-assisted technique over the totally laparoscopic approach for such major procedures in terms of safety, exposure, and oncological appropriateness. Furthermore, HALS can provide particular advantages in the case of malignancy, allowing for palpation of the tumor and manual staging, and in the case of voluminous cystic lesions, which can be more effectively removed en-bloc^[31-35].

The hand-assisted pancreatic resections were performed with the insertion of trocars along with a subcostal mini-laparotomy, through which the non-dominant hand was inserted to provide traction and direct palpation, while the demolition and reconstruction phase were both accomplished via laparoscopic instrumentation by the dominant hand. In the case of Pancreaticoduodenectomy (PD), all three anastomosis were performed intracorporeally^[30], which is also because mini-laparotomy is usually located in a position not favorable to be exploited for an open pancreatic anastomosis^[36].

The HALS approach was mostly used to perform Distal Pancreatectomy (DP) because it is a relatively easier procedure without need for complex anastomosis and therefore a greater effort has been put in trying to make this procedure as less invasive as possible. Initial experience with totally laparoscopic DP has been encouraging, stating a marked reduction of LOS, but, at the same time, relevant limitations were identified, such as a long operative time and a high conversion rate^[37,38]. At the beginning, trying to transition from a purely open approach to a totally minimally-invasive procedure, HALS appeared to be a good compromise, and several reports have been published stating its advantages^[39,40]. Postlewait *et al.*^[41] reported a lower

intraoperative blood loss and shorter hospital stay than open surgery and comparable perioperative and oncological outcomes. Gamboa *et al.*^[16] showed similar results and additionally reported a shorter operative time than totally minimally invasive approach, a similar LOS, and a lower conversion rate, even though patients undergoing hand-assisted distal pancreatectomy (HADP) had more comorbidities and a higher number of previous abdominal operations. Kneuert *et al.*^[42] reported the outcomes of laparoscopic DP (LDP) at their institution over an 11-year period; a reduced use of hand-assistance was observed with growing experience and a reduced LOS in TLS relative to HALS. A similar trend in reduction of HALS use over time was reported by Jayaraman *et al.*^[43] and Nakamura *et al.*^[44]. A relevant piece of literature includes HADP in the laparoscopic cases, and it is therefore difficult to extrapolate data on specific HADP outcomes^[45-52]. The current available literature on the topic is summarized in Table 1; articles where the surgical technique is not specified were excluded. Placement of trocars and hand-port is shown in Figure 1.

Some reports have postulated a non-inferiority of the hand-assisted approach for PD relative to open, but its usefulness has been questioned^[29,30,62-64]. In PD, the advantage of hand assistance does not appear to be striking. This is probably ascribable to the fact that the complex reconstruction phase, in HADP, is performed intracorporeally, and, if a surgeon has enough laparoscopic skills to perform the reconstructive part, he conceptually should not need the help of the hand in the demolition phase^[36]. Accordingly, recent literature reports a very limited adoption (0.6%) of the hand-assisted approach for PD^[36]. Some hybrid approaches have been proposed, with the demolition phase performed with a hand-assisted approach and the reconstruction phase with an open approach via a mini-laparotomy^[65].

LAPAROSCOPIC-ASSISTED SURGERY

A similar but somewhat different hybrid approach that appeared to be more suitable for PD is laparoscopic-assisted surgery (LAS). In LAS, the preparation and part of the demolition phase of the surgical operation is managed via laparoscopy, while the reconstruction part is performed out of the body via a small laparotomic incision^[66]. With this approach, we are able to take advantage of the improved vision of secluded spaces given by the laparoscopy, sparing a large incision to the patient and granting a faster postoperative recovery, while assuring an adequate anastomosis technique and hemostasis through a small incision that can also be used for the retrieval of the resected specimen^[67,68]. Several authors, in the initial phase of approaching minimally invasive PD, used a laparoscopic-assisted PD (LAPD) approach and reported their case series, proposing the feasibility of LAPD^[69-74]. LAPD showed non-inferior results to open surgery in terms of perioperative and oncological outcomes (comparable number of harvested lymph nodes and higher R0 rates)^[75]. Similar results were also reported by Tan *et al.*^[76] and Mendoza *et al.*^[77], who showed no differences in oncological and perioperative outcomes between open PD and LAPD. Tian *et al.*^[68] reported a lower estimated blood loss and shorter time to first flatus and Wang *et al.*^[67] described again a lower intraoperative blood loss and a shorter LOS. Additionally, a lower rate of anastomosis related complications has been reported compared to totally laparoscopic PD performed by experienced pancreatic surgeons at the beginning of their learning curve^[78]. Similarly promising results were reported by Deichmann *et al.*^[79]. No differences in intraoperative characteristics and postoperative outcomes were found between LAPD and robotic-assisted PD by Piedimonte *et al.*^[80]. Patel *et al.*^[81] reported a shorter LOS and lower severe morbidity rate and reoperation rate in LAPD compared to TLS, although a progressive shift from LAPD to TLS was observed over time. Somewhat similar results were published by Wang *et al.*^[82], reporting an increased operative time and blood loss in LAPD relative to TLS but similar LOS, morbidity rate, and postoperative pancreatic fistula (POPF) rate, with LAPD adopted by more inexperienced surgeons. In addition, Goh *et al.*^[83] reported a more frequent adoption of the hybrid technique during their early experience to allow for a safer transition to totally MIS. van Hilst *et al.*^[84] compared postoperative outcomes in LAPD and TLS without finding any significant difference; similar results were reported by

Table 1. Hand-assisted laparoscopic distal pancreatectomy

	Period of enrollment	Surgical operation	Included approaches	N of HALS pancreatic procedures	HALS vs. open	HALS vs. TLS/robotic
Cuschieri ^[29] , 2000	-	DP, TP, minor pancreatic resections, liver resections,	HALS	2	-	-
Misawa et al. ^[53] , 2006	2004-2005	DP	HALS, open	8	Reduced IBL, LOS Similar OT	-
D'Angelica et al. ^[39] , 2006	2002-2004	DP	HALS	17	-	-
Pierce et al. ^[54] , 2007	2000-2006	DP, enucleation	HALS*, TLS	3	-	-
Teh et al. ^[55] , 2007	2002-2005	DP	HALS*, TLS, open	8	-	-
Tang et al. ^[56] , 2007	1999-2006	DP	HALS*, TLS, open ^o	2	-	-
Nakamura et al. ^[44] , 2008	2000-2007	DP	HALS*, TLS, open	5	-	-
Laxa et al. ^[57] , 2008	2002-2007	DP	HALS, TLS	7	-	-
Vijan et al. ^[58] , 2010	2004-2009	DP	HALS*, TLS, open	2	-	-
Jayaraman et al. ^[43] , 2010	2003-2009	DP	HALS*, TLS, open	38	-	-
Gumbs et al. ^[59] , 2012	-	DP	HALS*, TLS	4	-	-
Kneuert et al. ^[42] , 2012	2000-2011	DP	HALS, TLS	62	-	Increased LOS
Rostas et al. ^[60] , 2012	2008-2011	DP	HALS	34	-	-
Rutz et al. ^[61] , 2014	2009-2013	DP	HALS, TLS, open	21	-	Increased IBL, tumor size Similar LOS, morbidity
Postlewait et al. ^[41] , 2018	2000-2014	DP	HALS, TLS, robotic, open	46	Reduced IBL, LOS Similar specimen length, OT, and LN yield	Similar IBL, LOS
Gamboa et al. ^[16] , 2020	2010-2018	DP	HALS, TLS, robotic, open	109	Reduced IBL, LOS Similar OT, morbidity, LN yield, RO rate	-

The literature search was conducted on the PubMed database. The search terms used were “laparoscopy” OR “hand-assisted” AND “pancreatic resection” OR “distal pancreatectomy” OR “pancreatectomy” individually or in combination. A manual search of reference lists of included articles was conducted. Case reports were excluded from the table. N: Number; HALS: hand-assisted laparoscopic surgery; TLS: total laparoscopic surgery; DP: distal pancreatectomy; TP: total pancreatectomy; LOS: length of stay; IBL: intraoperative blood loss; OT: operative time; LN: lymph node. *HALS was not treated as a separate group from laparoscopy; ^ohistorical cohort.

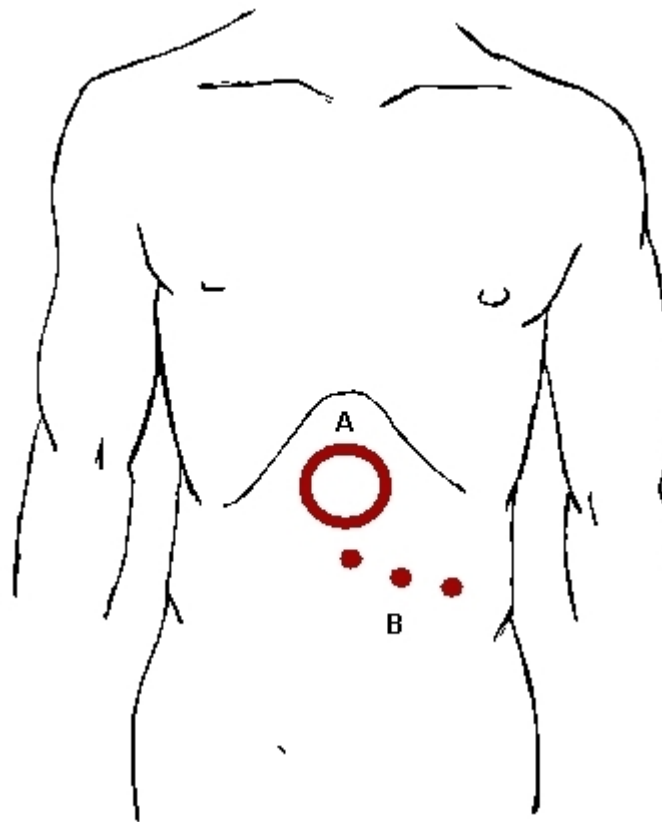


Figure 1. Trocars and hand-port placement in hand-assisted laparoscopic distal pancreatectomy. The placement of trocars widely changed among different reports. Proposed placement of trocars: (A) hand-port; and (B) ports for trocars placement.

Dulucq *et al.*^[85], Speicher *et al.*^[86] tracked the evolution of PD procedure over time at their institution, observing a progressive increase in the use of TLS over LAPD with growing experience and a parallel decrease of OT and complication rate; analogous findings were reported by Kim *et al.*^[87] and Lu *et al.*^[88]. The literature appears rather inhomogeneous, and it is difficult to draw definitive conclusions; however, in light of the reported data, the hybrid method appears to be safe and not inferior to the open approach^[69,70,89,90]. It also seems to provide some advantages over TLS in the early phase of the learning curve, but this may lose relevance in the case of surgeons with extensive experience in laparoscopy. A relevant piece of literature includes LAPD in the laparoscopic cases, and it is therefore difficult to extrapolate data on specific LAPD outcomes. The current available literature on the topic is summarized in Table 2; articles where the surgical technique is not specified were excluded. Placement of trocars and mini-laparotomy is shown in Figure 2.

MIS IN THE PANCREATIC SURGERY FIELD: WHERE ARE WE NOW?

Distal pancreatectomy

It is worth noting that, despite the initial setback, MIS has been greatly implemented in the pancreatic surgery field in recent years. Several observational studies, reviews, and metanalysis reported on the safety of minimally invasive distal pancreatectomy (MIDP) and proposed its advantages^[98-106]. A multicentric randomized controlled clinical trial comparing MIDP to open distal pancreatectomy demonstrated, despite a similar major complication rate, a reduced rate of delayed gastric emptying, a reduced intraoperative blood loss, a reduced time to functional recovery, and a better quality of life^[107]. In light of this evidence, MIDP has become the standard of care for benign and low malignant tumors^[108]. Regarding the use of

Table 2. Laparoscopic-assisted pancreaticoduodenectomy

	Period of enrollment	Surgical operation	Included approaches	N of LAS pancreatic procedures	LAS vs. open	LAS vs. TLS/robotic
Staudacher et al. ^[72] , 2005	2003-2004	PD	LAS	4	-	-
Dulucq et al. ^[85] , 2006	1999-2005	PD	LAS, TLS	9	-	Similar IBL, OT, LOS
Pugliese et al. ^[91] , 2008	2002-2006	PD	LAS*, TLS	7	-	-
Cho et al. ^[70] , 2009	2007-2008	PD	LAS	15	-	-
Machado et al. ^[92] , 2013	-	PD	LAS*, TLS	2	-	-
Kim et al. ^[87] , 2013	2007-2011	PD	LAS*, TLS	10	-	-
Lee et al. ^[73] , 2013	2009-2012	PD	LAS	42	-	-
Langan et al. ^[89] , 2014	2010-2013	PD	LAS, open	27	Reduced LOS Better QoL Similar OT, morbidity rate	-
Wang et al. ^[67] , 2014	2009-2013	PD	LAS, open	13	Decreased blood loss, LOS Similar complication and mortality rate	-
Wellner et al. ^[90] , 2014	1996-2013	PD	LAS, open	40	Decreased need for blood transfusions Similar complication and mortality rate	-
Speicher et al. ^[86] , 2014	2010-2013	PD	LAS, TLS, open	31	Increased IBL, POPF grade C rate Similar RO rate	Increased IBL, POPF grade C rate Similar RO rate
Liang et al. ^[93] , 2015	2011-2013	PD	LAS*, TLS, open	13	-	-
Piedimonte et al. ^[80] , 2015	2010-2014	PD	LAS, RA	14	-	Similar OT, IBL, morbidity rate
Wang et al. ^[54] , 2015	2010-2013	PD	LAS, TLS	6	-	Similar OT, IBL, morbidity
Mendoza et al. ^[77] , 2015	2014	PD	LAS, open	18	Reduced LOS Increased OT Similar IBL, LN yield, RO rate, morbidity rate, POPF rate	-
Liu et al. ^[71] , 2015	2011-2012	PD	LAS	21	-	-
Lu et al. ^[88] , 2016	2012-2015	PD	LAS*, TLS	9	-	-
Patel et al. ^[81] , 2017	2006-2016	PD	LAS, TLS	17	-	Reduced LOS, length of ICU stay, severe morbidity, reoperation rate
Kantor et al. ^[94] , 2018	2014-2015	PD	LAS*, TLS, robotic, open	304	-	-
Nassour et al. ^[95] , 2018	2014-2015	PD	LAS*, TLS, robotic, open	54	-	-
Deichmann et al. ^[79] , 2018	2000-2015	PD	LAS, open	60	Decreased OT, LOS, need for blood transfusions, CR-POPF rate	-

Kuesters <i>et al.</i> ^[75] , 2018	2010-2016	PD	LAS, open	62	Increased OT, RO rate Comparable lymph node yield, morbidity and mortality rate Shorter LOS	-
Tan <i>et al.</i> ^[76] , 2019	2014-2016	PD	LAS, open	20	Increased OT Similar morbidity rate, LN yield, RO rate Reduced time to deambulation	-
Goh <i>et al.</i> ^[83] , 2019	2014-2017	PD, TP	LAS*, TLS, robotic	18	-	-
van Hilst <i>et al.</i> ^[84] , 2019	2014-2018	PD	LAS, TLS	56	-	Increased conversion rate Similar IBL, OT, LOS, POPF rate, severe morbidity rate
Pham <i>et al.</i> ^[74] , 2020	2014-2019	PD	LAS	18	-	-
Tian <i>et al.</i> ^[68] , 2020	2013-2018	PD	LAS, open	36	Decreased blood loss Increased OT Similar CR-POPF rate, need for blood transfusions, LOS	-
Nieuwenhuijs <i>et al.</i> ^[78] , 2020	2016-2017	PD	LAS, open, TLS	10	Similar CR-POPF	-
Klompmaier <i>et al.</i> ^[96] , 2020	2012-2017	PD	LAS*, RA, TLS, open	130	-	-
Wang <i>et al.</i> ^[82] , 2020	2016-2018	PD	LAS, TLS	48	-	Increased OT, IBL Similar LOS, morbidity rate, POPF rate
Al-Sadairi <i>et al.</i> ^[69] , 2021	2019	PD	LAS	21	-	-

The literature search was conducted on the PubMed database; the search terms used were "laparoscopy" OR "laparoscopic-assisted" OR "hybrid" OR "hand-assisted" AND "pancreatic resection" OR "pancreaticoduodenectomy" OR "Whipple" or "pancreatectomy" individually or in combination. A manual search of reference lists of included articles was conducted. Case reports were excluded from the table. Articles with no full text available were excluded^[97]. Articles presenting new pancreatic anastomotic techniques were excluded. N: Number; LAS: laparoscopic-assisted surgery; TLS: total laparoscopic surgery; RA: robotic-assisted; PD: pancreaticoduodenectomy; TP: total pancreatectomy; LOS: length of stay; IBL: intraoperative blood loss; OT: operative time; QoL: quality of life; CR-POPF: clinically relevant postoperative pancreatic fistula. *LAS was not treated as a separate group from laparoscopy.

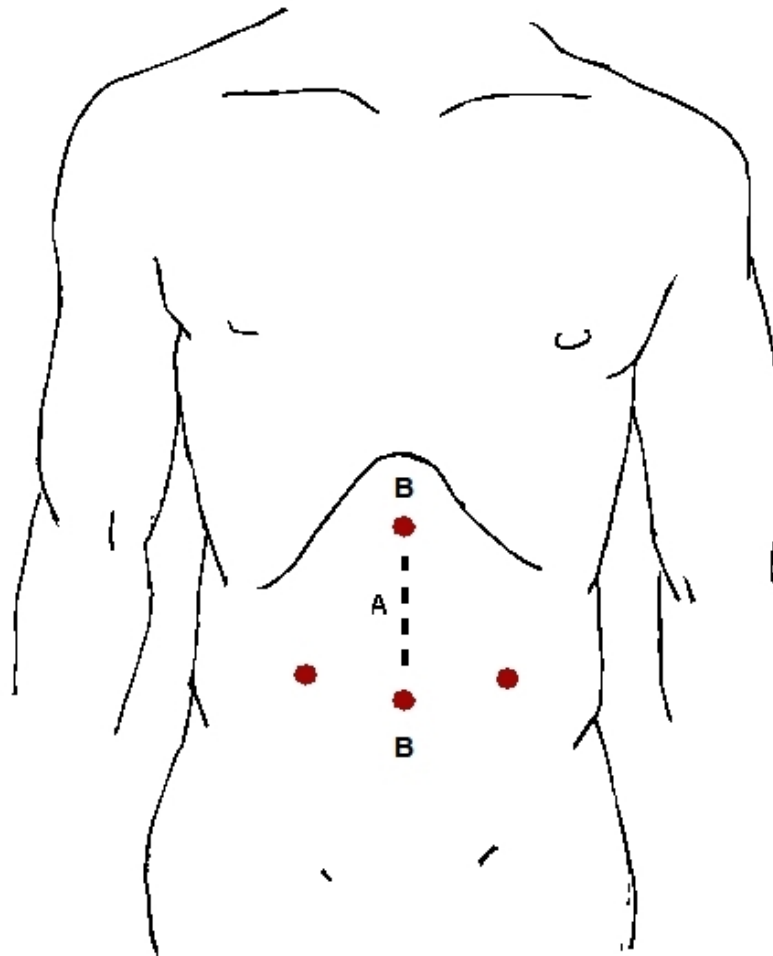


Figure 2. Trocars and mini-laparotomy placement in laparoscopic-assisted pancreaticoduodenectomy. The placement of trocars widely changed among different reports. Proposed placement of trocars: (A) mini-laparotomy; and (B) ports for trocars placement.

MIDP for the treatment of pancreatic ductal adenocarcinoma, available data suggest the oncological appropriateness of the procedure, but high-level evidence is still lacking. Oncological outcomes were comparable in terms of resection margins, disease free survival, and overall survival, while the number of harvested lymph nodes was found to be lower in one metanalysis and comparable in a second one^[101,109,110]. The DIPLOMA trial^[111] showed a higher R0 resection rate for MIDP, a less frequent Gerota's fascia resection, a lower number of harvested lymph nodes, and a comparable median survival. Randomized clinical trials are ongoing, trying to give a definitive answer. Regarding the choice of the type of MIS technique, several observational studies have been published comparing the robotic versus laparoscopic approach. Theoretically, the robotic platform should provide advantages in terms of improved dexterity and vision, allowing for completion of more complex procedures, but whether this translates into better outcomes and cost-effectiveness in clinical practice is still controversial^[112]. Reported outcomes in the literature are heterogeneous: recent metanalyses showed a higher rate of splenic vessel preservation and a lower conversion rate, but higher cost in Robotic DP compared to LDP^[113,114]. Another metanalysis reported a shorter LOS and an increase of spleen preservation rate at the expense of increased cost^[115]. Oncological and postoperative outcomes, such as POPF rate and overall morbidity, were comparable. Other studies showed no major differences in perioperative outcomes^[116-118]. Therefore, the Miami Guidelines conclude that both laparoscopic and robotic DP are considered valuable and equivalent options, and the choice

between the two depends on the preference of the surgeon and his familiarity with the technique^[108].

Pancreaticoduodenectomy

Pancreaticoduodenectomy is still performed in the majority of centers with an open approach due to its technical difficulty and the complex reconstructive phase. Available data on safety and feasibility of MIPD are conflicting. Reports from low-volume centers showed an increased morbidity and mortality after MIPD^[119,120], while experience in high-volume centers demonstrated a similar rate of mortality and morbidity compared to OPD. Moreover, in high-volume centers, LPD showed a lower rate of DGE, decreased blood loss, and a shorter hospital stay but a longer operative time^[36,121,122]. Three randomized clinical trials have been published with mixed results. Palanivelu *et al.*^[123] showed similar oncological and perioperative outcomes in OPD and LPD. Conversely, the LEOPARD-2 trial was interrupted early because of safety concerns due to a disproportionately high number of deaths in the LPD arm^[124], while the PADULAP trial reported a lower major complication rate and a shorter LOS and similar oncological outcomes^[125]. No major differences in outcomes have been reported between LPD and RPD^[126,127]. In view of existing evidence, the Miami Guidelines concluded that insufficient data exist to recommend MIPD over OPD. MIPD appears to be safe and feasible but only if performed by surgeons who have completed the learning curve and if set in high-volume centers experienced in both pancreatic surgery and MIS.

HALS: DOES IT STILL HAVE A ROLE IN PANCREATIC SURGERY PRACTICE TODAY?

Analysis of trends in the use of MIS in pancreatic surgery showed how, with time, we had a steep increase of MIDP, and the increase in number was paralleled by increasing complexity of procedures and a decrease in conversion rate and operative time^[42]. Moreover, the proportion of procedures performed with hand assistance decreased with time as surgeons became more skilled in MIS. It is worth noting that a recent analysis showed that MIDP is only used in one third of eligible patients^[128]. Therefore, on the one hand, HADP plays a very marginal role in high-volume centers, where surgeons have finished their learning curve, while, on the other hand, there are still centers in the process of implementation of MIS where HADP may play a fundamental role as a bridge to totally MIDP, easing the transition and shortening the learning curve. Moreover, HADP, with its shorter operative time, may be preferred in patients with multiple cardiological, pulmonary, and renal comorbidities who would not tolerate well the effects of prolonged anesthesia and pneumoperitoneum^[16]. Furthermore, HADP may be used as an intermediary step in conversion from MIDP to open in complex cases where manual assistance or tactile feedback is required or in the case of intraoperative complications because it appears that converted hand-assisted cases have a lower estimated blood loss and a shorter LOS than open^[16,30].

The role of MIS in PD is still not defined; MIPD can be performed in high-volume centers by experienced surgeons with acceptable outcomes, but the results are difficult to be generalized. In the process of the implementation of MIPD, LAPD may play a role as a bridge to totally laparoscopic PD allowing for a safer transition^[129,130].

In conclusion, the choice of the right approach needs to be tailored to the patient with a focus on his or her safety and to the surgeon keeping in mind his or her limits and expertise.

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Authors' contribution

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Ethical approval and consent to participate

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Consent for publication

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Technical Note

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Technique of robotic first rib resection for thoracic outlet syndrome

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Abstract

Conventionally, resection of the first rib has been performed by the transaxillary and supraclavicular approaches. These approaches are hampered by poor visualization and exposure of the operative field, neurovascular complications, and less than optimal surgical outcomes. The Robotic Surgical System allows for high-definition, magnified, three-dimensional visualization of the operative field and is associated with accurate instrument maneuverability in a confined space. Importantly, the robotic transthoracic technique facilitates the disarticulation of the costo-sternal joint, which appears to be the most critical determinant of surgical success. Robotic first rib resection has been associated with the best-reported outcomes in patients with both Neurogenic and Venous (Paget Schroetter Syndrome) Thoracic Outlet Syndrome (TOS). This paper outlines the technique of robotic first rib resection with disarticulation of the costo-sternal joint for patients with TOS.

Keywords: Robotic Surgery, first rib resection, thoracic outlet syndrome, neurogenic, venous, paget schroetter

INTRODUCTION

Thoracic Outlet Syndrome (TOS) is highly underdiagnosed and undertreated^[1]. It is estimated that TOS affects 0.3 to 8% of the population. This high variance in the reported prevalence reinforces the challenges in terms of understanding TOS. Any discussion about TOS always begins with the classification that dates back to the 1950s: Neurogenic (NTOS), Venous (Paget Schroetter Syndrome, PSS), and Arterial TOS^[2].



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Over the years, due to the lack of objective findings in the majority of patients with NTOS, NTOS has been further classified as True NTOS and Disputed (NTOS). The majority of patients with TOS have NTOS, and the majority of patients with NTOS are in the “Disputed” category (DNTOS). Patients with DNTOS have neurologic symptoms such as pain and paresthesia in the upper extremity, neck and shoulder with a normal neurologic exam and nerve conduction studies. Historically, it has been thought that TOS results from the compression of the neurovascular structures in the upper chest and the neck. The first rib has been the common denominator in this hypothesis.

Recently Gharagozloo *et al.*^[3,4] have described a congenital malformation at the costo-sternal joint of the first rib as the “offending” pathologic entity in patients with PSS and DTNOS [Figures 1-4]. Using dynamic Magnetic Resonance Imaging and 3-D computerized tomography reconstruction, these authors have shown that with the elevation of the upper extremity and activity, the subclavian vein is compressed between the costo-sternal joint and the clavicle. They have hypothesized that in patients with DNTOS, neurologic symptoms may manifest nerve pain that results from venous compression and the resultant venous ischemia of the nerves in the upper extremity. This hypothesis is based on the fact that the upper extremity is fed by a single artery and vein as an “end organ”. Venous congestion may be an essential factor precipitating circulatory disturbance in nerve roots and inducing neurogenic intermittent claudication. Venous congestion has been shown to break the blood-nerve barrier and result in relative ischemia^[5]. As a proof of concept, these authors have demonstrated that in patients with persistent neurologic symptoms following first rib resection, the disarticulation of the costo-sternal joint, which was previously described as the costoclavicular ligament, has resulted in excellent relief of symptoms^[6-8]. Therefore, it is crucial to disarticulate the costo-sternal joint as part of first rib resection in patients with TOS. Also, these authors have shown that PSS is simply the manifestation of the same pathologic entity, which results in thrombosis with prolonged compression of the subclavian vein.

The most common first rib resection is performed using a transaxillary or supraclavicular approach. However, these approaches are associated with neurovascular complications, incomplete decompression of the subclavian vein and the medial aspect of the thoracic outlet, and difficulty in disarticulating the costo-sternal joint from outside the chest cavity.

The robotic surgical systems have the advantages of 3D visualization and precise instrument maneuverability in a confined space. The surgical robot has facilitated a precise, minimally invasive transthoracic approach to disarticulating of the costo-sternal joint and resection of the first rib. This approach has been associated with the best-reported results in patients with PSS and NTOS.

This communication outlines the technique of robotic first rib resection with disarticulation of the costo-sternal joint for patients with TOS.

TECHNIQUE OF ROBOTIC RESECTION OF THE MEDIAL ASPECT OF THE FIRST RIB AND DISARTICULATION OF THE COSTO-STERNAL JOINT

A video of the procedure is available at: <https://www.youtube.com/watch?v=2mCKcgAAjbs>

Patients are placed in the lateral decubitus position with the affected side up with single lung ventilation of the ipsilateral side. The procedure is performed in 5 steps.

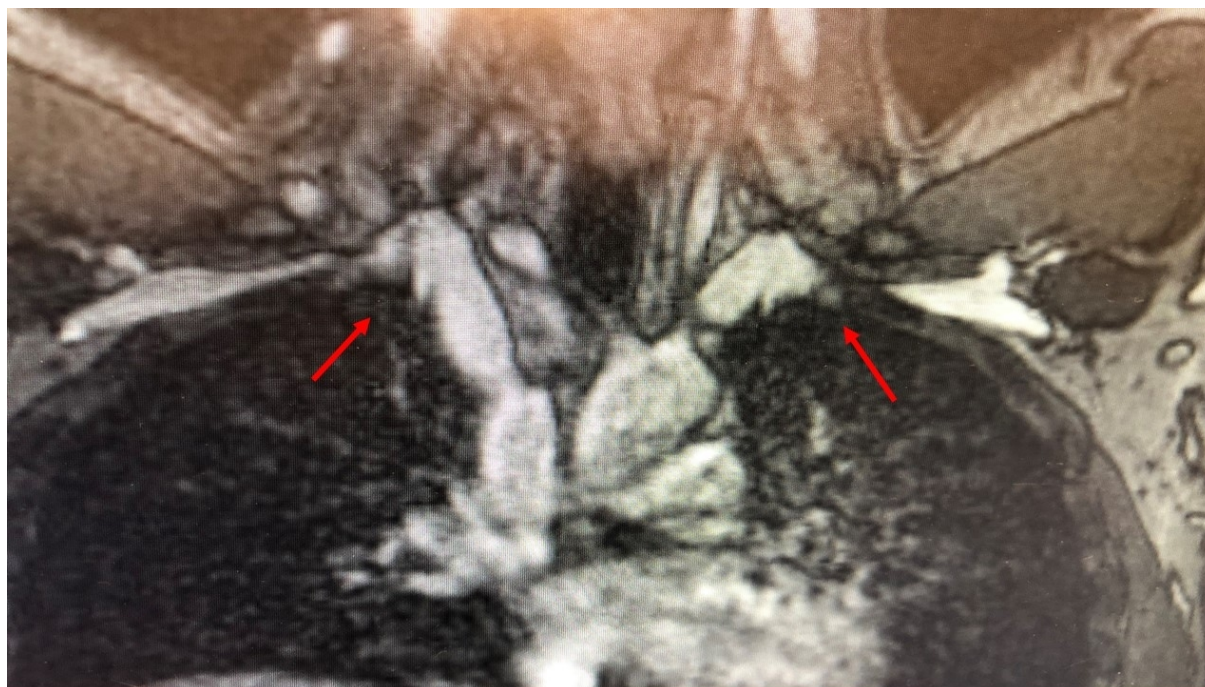


Figure 1. Magnetic Resonance Angiogram with elevation of the arms in a patient with PSS. There is bilateral compression off the subclavian-innominate junction (arrows). PSS: Paget schroetter syndrome.

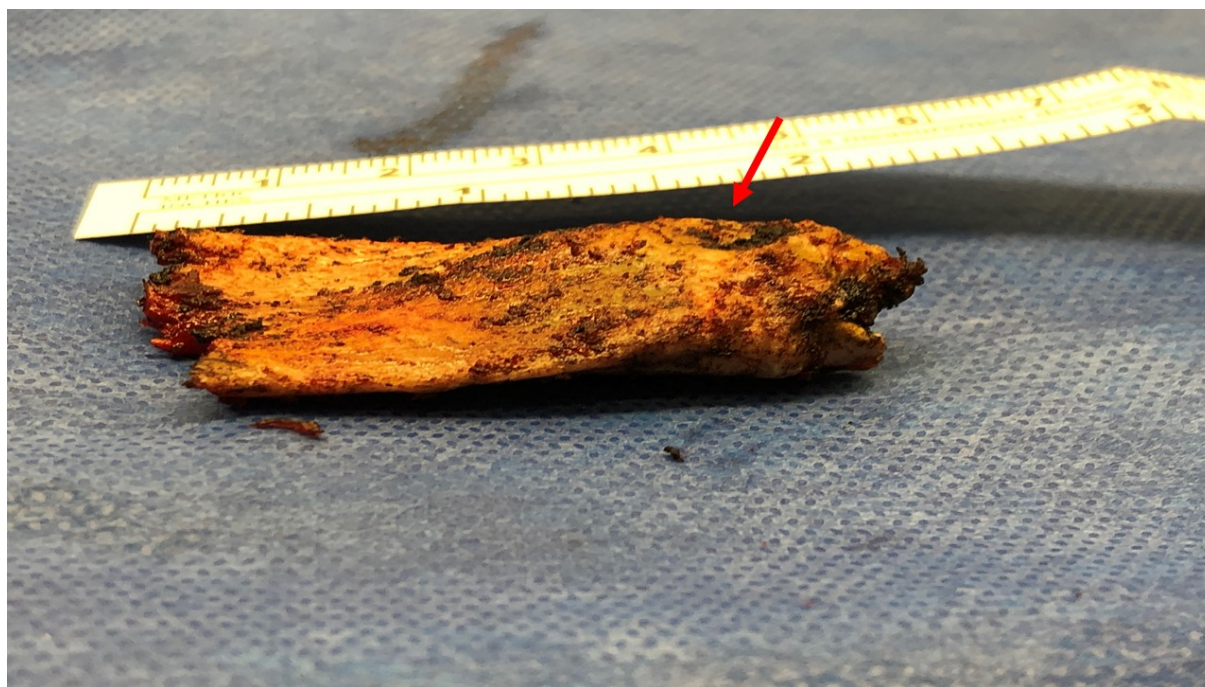


Figure 2. Resected “offending” portion of the right first rib showing a tubercle (arrow) and abnormal costo-sternal joint corresponding to the extrinsic compression seen in [Figure 1](#).

Step 1 - port placement

Three 2-cm, nontrocar incisions are made [[Figures 5-7](#)]. Incision #1 is made at the 5th intercostal (IC) space

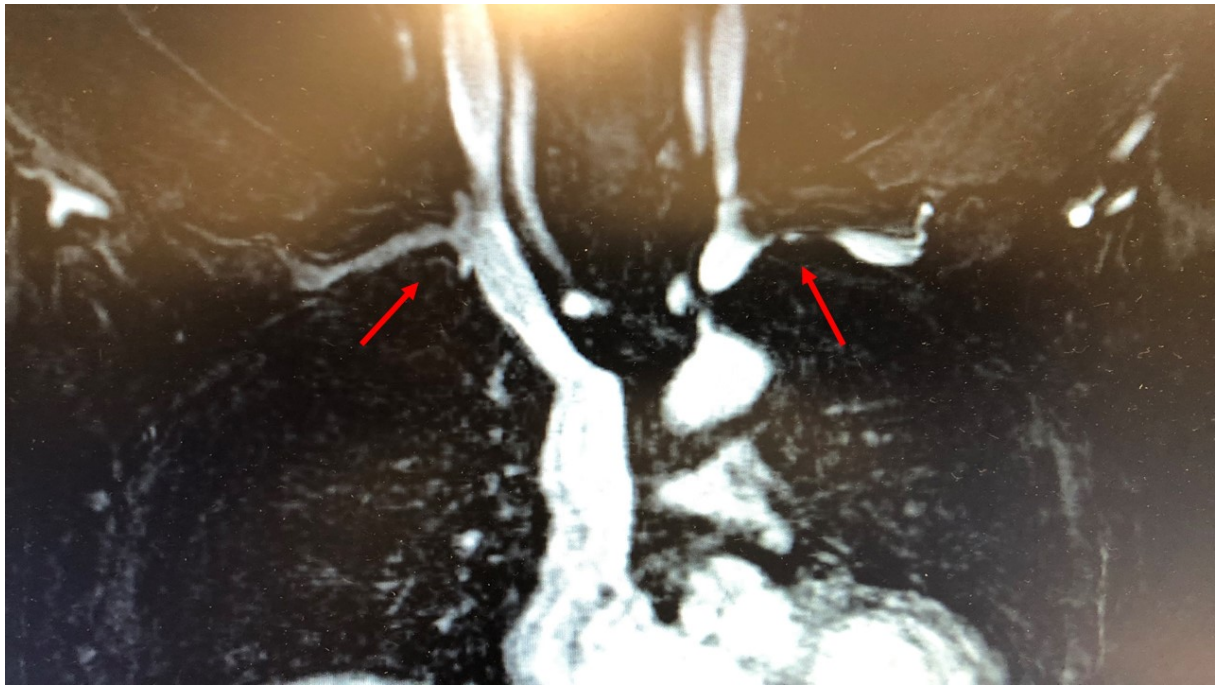


Figure 3. Magnetic Resonance Angiogram with elevation of the arms in a patient with DNTOS. There is bilateral compression off the subclavian-innominate junction (arrows). DNTOS: Disputed neurogenic thoracic outlet syndrome.



Figure 4. Resected “offending” portion of the right first rib showing a tubercle (arrow) and abnormal costo-sternal joint corresponding to the extrinsic compression seen in [Figure 3](#).

at the midaxillary line in the right chest. Incision #2 is made in the 4th IC space at the anterior axillary line. Incision #3 is made in the 4th IC space at the posterior axillary line. In the Left Chest, the port placement is

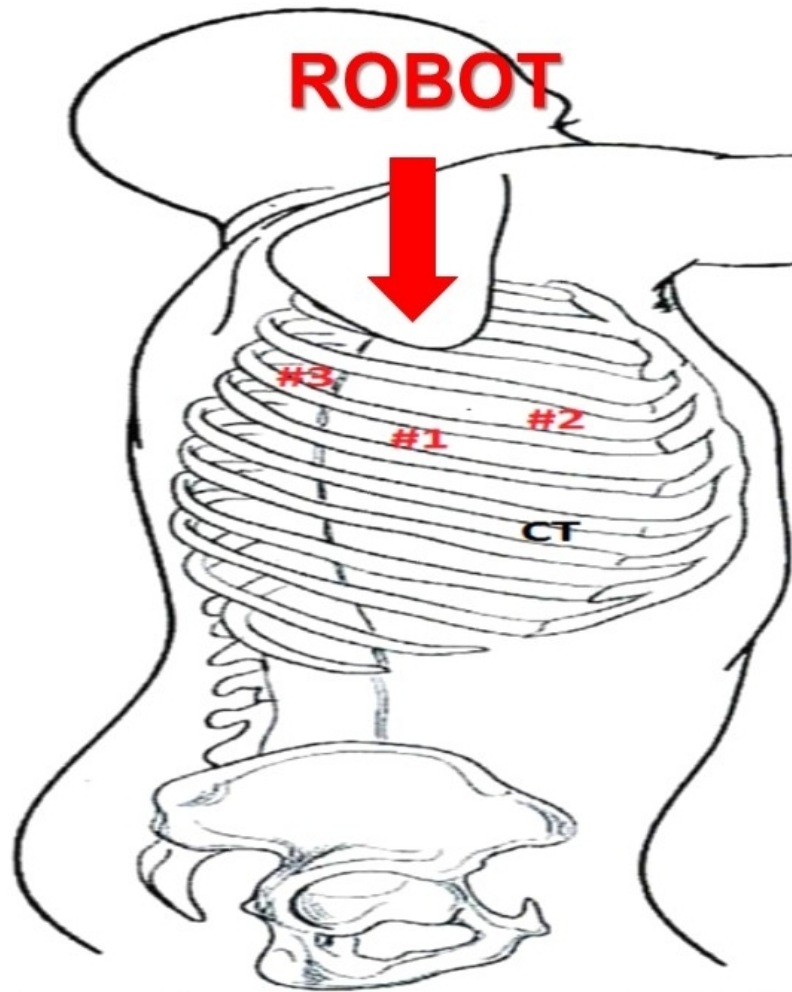


Figure 5. Patient in the left lateral decubitus position. Trocar sites are shown. The robot is brought over the head of the patient.

a mirror image of the right chest. A 1-cm incision #4 is made in the 6th intercostal space at the anterior axillary line. A retractor (Endopaddle Retractor; Auto Suture, Covidien incorporated, Mansfield, MA) is introduced through this incision and used to retract the lung inferiorly. At the end of the procedure, a chest drain (28 French tubes) is inserted through this incision.

Step 2 - dissection of the first rib

The surgical robot (da Vinci, Intuitive Surgical, Inc., Sunnyvale, CA) is positioned over the patient's head. The camera is placed in incision #1. For the placement of instruments, a 30-degree down-viewing camera is used. The right robotic arm with a hook cautery is positioned in incision #2. The left robotic arm with a grasper is positioned in incision #3. The assistant places a suction catheter through incision #3 under the left robotic arm. Next, the camera is turned to be 30-degree up viewing. The costo-asternal joint is identified. Then the pleura overlying the first rib is dissected. The edges of the rib are identified, as is the costo-sternal joint. Dissection of the pleura is carried just lateral to the subclavian artery. The lateral and posterior aspect of the rib with the associated neurologic structures is left intact.

Step 3 - division of the first rib

Next, the robotic arms are withdrawn. A 30-degree Video-assisted thoracic surgery camera is introduced,



Figure 6. Patient in the left lateral decubitus position. Trocar sites are shown. The robot (da Vinci Xi) is brought over the head of the patient.



Figure 7. Patient in the left lateral decubitus position. The retractor (arrow) which is fixed to the bed is used to retract the lung inferiorly.

and the rib under the subclavian artery is divided using a 6-mm thoroscopic Kerrison bone cutter (Depuy Inc., Raynham, MA). The area under the subclavian artery, which corresponds with the subclavian groove, is the thinnest portion of the rib and is amenable to division with the bone cutter. The rib's division at its

midpoint allows it to be pivoted on the costo-sternal and costovertebral joints in a trap door configuration.

Step 4 - robotic dissection of the first rib and disarticulation of the costo-sternal joint

The robotic arms are replaced in the same ports. A 30-degree down-viewing robotic camera is introduced through incision #1, a hook cautery is placed in the right robotic arm in incision #2, and a second hook cautery is placed in the left robotic arm in incision #3. The hook in the left arm is used to put downward traction on the rib as the hook cautery (30 cut/30 coagulation setting) is used to dissect the first rib away from the subclavian vein, disconnect the scalene muscles from the rib, and disarticulate the rib from the sternal and times clavicular joint [Figure 8]. During this dissection, the table assistant places upward pressure on the tissues just superior to the edge of the first rib. This maneuver moves the vascular structures away from the bone and facilitates the dissection. The resected rib is removed through incision #2.

Step 5 - analgesia and chest closure

After completing the robotic procedure and undocking the robot, subpleural catheters are introduced for a prolonged paravertebral block of intercostals 2 through 8. This technique has been described previously^[9]. This strategy for pain control continues even after the patient is discharged from the hospital and gives the patient 10 days of local pain control.

RESULTS

The results of robotic first rib resection for PSS and NTOS have been reported previously^[6,7,8]. A total of 162 patients have undergone robotic first rib resection by our group. The first rib was removed en bloc, and the costo-sternal joint was disarticulated. Operative time was 87.6 min +/- 10.8 min. There were no intraoperative complications. Hospital stay ranged from 2 to 4 days with a median hospitalization of 3 days. There were no neurovascular complications. There was no mortality. In patients with neurologic symptoms, immediate relief of symptoms was seen in 71/79 patients (91%). In these patients, Quick DASH Scores (Mean +/- SEM) decreased from 60.3 +/- 2.1 preoperatively to 5 +/- 2.3 in the immediate postoperative period, and 3.5 +/- 1.1 at 6 months ($P < 0.0001$)^[10]. In patients with Paget-Schroetter syndrome, 31% required endovascular venoplasty to completely open the subclavian vein after relieving the extrinsic bony compression. In patients with PSS, at 3, 6, 12, and 24 months, in all patients, MRA with maneuvers showed relief of extrinsic compression and patency of the subclavian vein. Two years after robotic resection of the offending portion of the first rib and obtaining patency of the subclavian vein, all patients remained asymptomatic and had full function of the affected upper extremity.

DISCUSSION

Historically, TOS has been poorly understood^[11,12]. Invariably discussion about TOS leads to cervical ribs. Cervical ribs and associated bands can compress the brachial plexus and subclavian artery in the neck. However, cervical ribs and the associated bands extending from the cervical rib to the first rib are rare and not a common cause of TOS. In fact, it has been suggested that cervical rib disease should be classified separately from TOS. In an attempt to unify neurovascular symptoms related to the upper extremity, in 1956, Peet^[13] proposed the term "Thoracic Outlet Syndrome". Unfortunately, in 1958, Rob and Standeven used a similar term, "Thoracic Outlet Compression Syndrome", in their description of a series of patients with cervical ribs, arterial thrombosis, and distal gangrene of the upper extremity^[14]. This inadvertent association between patients who would best be classified as Cervical Rib Disease, and patients with problems related to the thoracic outlet, has resulted in a great deal of confusion among medical practitioners. In order to better understand the pathogenesis of TOS and design appropriate surgical procedures for the treatment of this disease, patients with neurovascular symptoms of the upper extremity who have been previously classified as TOS should be separated into Cervical Rib Disease, and Thoracic

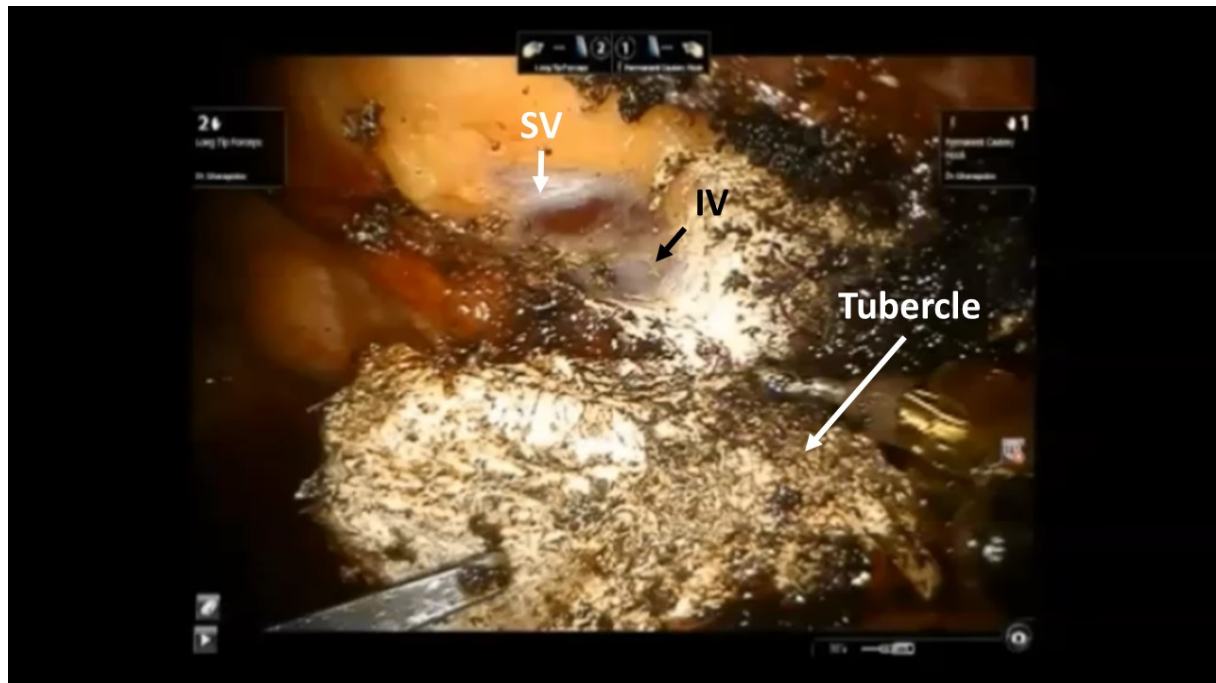


Figure 8. Intraoperative photograph during the robotic resection of the medial right first rib in a patient with Disputed Neurogenic TOS. The abnormal bony tubercle at the costo-sternal joint results in compression of the subclavian vein (SV) at its junction with the innominate vein (IV). TOS: Thoracic outlet syndrome.

Outlet Syndrome or “Subclavian Vein Compression Syndrome”. Gharagozloo *et al.*^[4] have proposed that symptoms which were previously classified as Neurogenic and Venous (PSS) TOS represent a variable symptomatic presentation of the compression of the subclavian vein by an abnormal bony tubercle at costo-sternal joint, which results in neurologic symptoms with mild compression (Neurogenic TOS) and thrombosis of the vein with prolonged compression (PSS). As a proof of concept, robotic resection of the medial aspect of the first rib and disarticulation of the costo-sternal joint has been associated with excellent results.

The robotic resection of the first rib has a number of technical challenges. These challenges can be divided into:

1. Anesthesia management: it is important to use hand ventilation with minimal mediastinal excursion during the robotic dissection. It prevents injury to the phrenic nerve or the superior vena cava.
2. Rib dissection: the costo-sternal joint for the first rib is invariably abnormal. The first rib should be identified at the costo-sternal joint and traced posteriorly. The first rib is covered with pleura and inner intercostal muscles. It is important to delineate the edges of the first rib clearly. In addition, the subclavian groove should be identified by tracing the subclavian artery from inside the chest. The Kerrison instrument is ideal for dividing the rib at the subclavian groove, where the rib is the thinnest. The anvil of the Kerrison instrument protects the subclavian artery while the blade divides the bone. The use of powered instruments or a Gigly saw has been described by Strother and Margolis^[15]. However, we have found the Kerrison to be the safest instrument for rib division.

3. Vascular injury: care should be taken to stay away from the subclavian vessels by remaining close to the bone. The surgical robot does not allow the use of two hook instruments. Therefore during this phase, the hook in the right robotic arm needs to be connected to an external cautery power source. The left hook pulls down on the bone, and the right hook “hugs” the bone. We have never had a vascular injury. However, we are always prepared and run team drills in a regular interval. Based on laboratory studies, the best way to control bleeding from the subclavian vein is to use the technique that we have previously described for control of major vascular injury during robotic lobectomy^[16].

Conclusion

Robotic surgical system allows for a minimally invasive, highly accurate approach to the disarticulation of the costo-sternal joint and resection of the abnormal portion of the first rib. The result following robotic first rib resection has been the best to date.

DECLARATIONS

Authors' contributions

Collected the data, designed and performed the procedures, and composed the manuscript: Gharagozloo F, Atiquzzaman N, Meyer M, Werden S

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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Original Article

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Hair loss in sleeve gastrectomy subjects: effects of designed supplements for nutritional deficiencies

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Abstract

Aim: Hair loss is a common complication after bariatric surgery that is related to nutritional deficiencies. The aim of this study was to evaluate the prevalence of micronutrient deficiencies preoperative and postoperative and their relationship with hair loss 12 months after bariatric surgery (BS) in those younger and older than 45 years of age, with or without a prescription for supplements.

Methods: In this prospective study, performed between 2018 and 2020 on patients undergoing laparoscopic sleeve gastrectomy (LSG) (not generally BS) in our hospital, the patients were categorized into two main groups of with or without a prescription for supplements. In addition, each main group was divided into age subgroups. Then, complete clinical and biological nutritional assessments were performed in these four subgroups, before and after surgery. Hair loss related to nutritional deficiencies were systematically recorded at 12 months after LSG.

Results: In total, 1224 patients undergoing LSG were enrolled into the study. Nutritional deficits in some variables were even tripled after LSG in both the younger and older groups without a prescription for supplements. In the group with a prescription for supplements, nutritional deficiencies declined postoperatively. The postoperative deficits in the group without a prescription for supplements were frequently in iron (41.83% for younger group; 44.44% for older group) and zinc (42.15% for younger group; 43.79% for older group). In the group with a prescription for supplements, hair loss was less common than in the group without a prescription for supplements postoperatively.



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Conclusion: Preoperative monitoring of the combination of several nutritional deficits could be used to identify patients at risk and prevent the onset of deficiencies and their consequences after BS. Identification and correction of micronutrient deficiencies were essential for treating hair loss.

Keywords: Sleeve gastrectomy, hair loss, older ages

INTRODUCTION

The prevalence of obesity, over the last three decades, has tripled with an estimated 13% of adults being obese in 2016^[1]. Obesity is not only a cosmetic concern but also a medical problem that increases the risk of other diseases, such as diabetes, atherosclerotic cardiovascular diseases, high blood pressure, and some kinds of cancers^[2-5]. According to the World Health Organization (WHO), obesity is defined as “abnormal or excessive fat accumulation that presents a risk to health”^[6]. Obesity results from a combination of inherited factors, environmental and socioeconomic factors, personal diet, and exercise choices^[7].

Bariatric surgery has evolved in the United States and worldwide over the past two decades and is done to help patients lose excess weight and reduce the risk of potentially life-threatening weight-related health problems. Bariatric surgery is a method of treatment that can be used in the case of patients with BMI ≥ 35 kg/m² and coexisting complications of obesity, such as arterial hypertension, or with BMI ≥ 40 kg/m² for normal individuals^[8]. The two most commonly performed bariatric surgery procedures are Roux-en-Y gastric bypass and sleeve gastrectomy (SG)^[9-11]. However, these methods are not free from complications, and the most common ones are micronutrient deficiencies because of preoperative malnutrition, decreased food intake due to reduced hunger, and increased satiety and food intolerance or vomiting^[12]. Some of these deficiencies cause severe clinical impacts, including neurological complications, anemias, bone demineralization, and protein malnutrition^[13-15]. Moreover, many patients have symptoms suggestive of nutritional deficiencies after BS, but there are few prospective studies to specify their prevalence after surgery^[13-16]. The frequently reported complications in studies are hair loss, cramps, and paresthesia. These symptoms are more frequent in subjects who are noncompliant to medical visits in the long term after surgery^[11].

The main aim of our study was to assess the link between symptoms suggestive of nutritional deficiencies such as hair loss and a large panel of nutritional parameters in subjects who underwent bariatric surgery.

METHODS

In this prospective study performed on LSG candidates from 2018 to 2020, we included consecutive male and female subjects who underwent LSG at our institution and with complete clinical and biological nutritional assessments performed in Erfan Hospital. The subjects were studied were divided into those younger and older than 45 years of age, with or without a prescription for supplements. Multivitamin supplements were systematically prescribed after surgery, and the reference ranges were recommended by the dietetics and nutritional experts based on age and gender. Hair loss related to nutritional deficiencies was systematically recorded at the 12-month follow-up visit after LSG. Hair loss was defined as either an enhanced amount of hair falling out daily (effluvium) or visible hairlessness (alopecia). Normal hair loss (normal shedding) was referred to the loss of up to 100 hairs per day. Biological parameters (including vitamins B1, B12, C, A, E, and D and minerals iron, folic acid, biotin, riboflavin, zinc, and selenium) were assessed using routine techniques^[11,17,18]. 25-hydroxy vitamin D was assayed with a liquid chromatography-tandem mass spectrometry method (Waters Ltd., Elstree, UK). Vitamins A and E were carried out using a high-performance liquid chromatography technique (Agilent Corporation, Santa Clara, CA, USA). Trace

elements were measured using inductively coupled plasma mass spectrometry (Agilent). Other routine chemistry and hematology analyses were measured on automated platforms (Abbott Diagnostics, Maidenhead, UK; Hobira Medical, Montpellier, France respectively). The daily doses of supplements for patients younger than 45 years of age include: 8 mg of iron for men and post-menopausal women, 18 mg of iron for menstruating women, 30 µg of biotin, 11 mg of zinc for men and 8 mg of zinc for women, 55 µg selenium, 400 µg of folic acid, 2.4 µg of riboflavin and vitamin B12, 1.2 mg of vitamin B1 for men and 1.1 mg of vitamin B1 for women, 900 mcg of vitamin A for men and 700 mcg of vitamin A for women, 15 mg of vitamin E, 45 mg of vitamin C, and 15 mcg of vitamin D. The only differences in the daily doses of supplements in subjects older than 45 years of age were for iron and zinc, which were prescribed at 18 and 11 mg, respectively. More details on the composition of the multivitamin supplement are given in [Table 1](#). Patients initiated supplementation two weeks after surgery and continued for two months. Compliance with supplementation was carefully assessed by the medical follow-up team. This study obtained the ethic code EN2H11935642287TA through the Ethical Board of Erfan Niayesh Hospital.

Surgical technique

All LSG procedures were carried out by a longitudinal resection from the angle of His to around 3-4 cm orally to the pylorus using a 36-French bougie inserted along the lesser curve. More details on surgical technique have been published previously^[19].

Statistical analysis

All descriptive findings are presented as mean/median and standard deviation for quantitative variables and count and percentage for qualitative variables. After checking the normality of variables using histogram graphs and the Kolmogorov-Smirnov test, the Wilcoxon rank test was used to compare the non-parametric variables and *t*-test to compare other continuous variables before and after LSG. The statistical significance level was defined as 0.05 ($\alpha = 0.05$). The statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL).

RESULTS

For all sleeve gastrectomy candidates in our center, we routinely invited patients to participate in this study. We tried to distribute subjects equally into two groups of males and females and two subgroups of those younger and older than 45 years of age. Of 1224 patients, 612 cases were females (50.0%) and 612 subjects were males (50.0%), ranging from 21 to 75 years of age with 612 (50.0%) under 45 years and 612 (50.0%) over 45 years.

Prevalence of preoperative nutritional deficiencies

Nutritional deficiencies are common issues in morbidly obese subjects. In this prospective study, we recorded every potential deficiency in micronutrients at the first visit before surgery. The most prevalent micronutrients with deficiency in those younger than 45 years were iron (29.9%), vitamin D (28.1%), zinc (27.94%), vitamin A (24.01%), and vitamin C (20.9%). Among those older than 45 years, zinc (27.94%), iron (25.98%), vitamin A (25.81%), vitamin E (25%), vitamin C (23.69%), and vitamin D (23.03%) were the most common deficits before surgery.

Prevalence of postoperative nutritional deficiencies

Nutritional deficits were observed after BS in both age groups without a prescription for supplements (first group, younger than 45 years of age; second group, older than 45 years of age) [[Table 1](#)]. Deficits in the group without a prescription for supplements were frequently in iron (41.83% for first group; 44.44% for second group), zinc (42.15% for first group; 43.79% for second group), and vitamin A (61.76% for first group; 58.82% for second group). In the group with a prescription for supplements, nutritional deficiencies

Table 1. Prevalence of micronutrient deficiencies in those younger and older than 45 years of age, with or without a prescription for supplements before surgery and at 12 months after LSG

Variables	Normal levels of micronutrients in normal individuals	Younger than 45 years of age					Older than 45 years of age				
		Pre operative deficiency	Post operative deficiency without supplement	Supplements dose - daily intake	Post operative deficiency with supplement	P-value ¹	Pre operative deficiency	Post operative deficiency without supplement	Supplements dose - daily intake	Post operative deficiency with supplement	P-value ²
<i>n</i>	-	612	306	-	306	-	612	306	-	306	-
Iron	M: 80-180 mcg/dL F: 60-160 mcg/dL	183 (29.9%)	128 (41.83%)	Men and post-menopausal women: 8 mg Menstruating females: 18 mg	85 (27.77%)	0.00026*	159 (25.98%)	136 (44.44%)	18 mg	77 (25.16%)	< 0.00001*
Biotin	133-329 pmol/L	60 (9.8%)	103 (33.66%)	30 µg	48 (15.68%)	< 0.00001*	66 (10.78%)	116 (37.9%)	30 µg	32 (10.45%)	< 0.00001*
Zinc	0.66-1.10 mcg/mL	171 (27.94%)	129 (42.15%)	M: 11 mg F: 8 mg	58 (18.95%)	< 0.00001*	171 (27.94%)	134 (43.79%)	11 mg	55 (17.94%)	< 0.00001*
Selenium	70-150 ng/mL	84 (13.72%)	52 (16.99%)	55 µg	45 (14.7%)	0.4413	91 (14.86%)	61 (19.93%)	55 µg	48 (15.68%)	0.1706
Folic acid	2.7-17.0 ng/mL	48 (7.84%)	39 (12.74%)	400 µg	27 (8.82%)	0.1187	55 (8.98%)	42 (13.72%)	400 µg	25 (8.16%)	0.0278*
Riboflavin	4-24 µg/dL	74 (12.09%)	41 (13.39%)	2.4 µg	33 (10.78%)	0.3221	79 (12.90%)	46 (15.03%)	2.4 µg	26 (8.49%)	0.0120*
Vitamin B12	200-900 pg/mL	72 (11.76%)	42 (13.72%)	2.4 µg	24 (7.84%)	0.018*	96 (15.68%)	60 (19.6%)	2.4 µg	39 (12.74%)	0.0208*
Vitamin B1	2.5-7.5 µg/dL	18 (2.94%)	18 (5.88%)	M: 1.2 mg F: 1.1 mg	6 (1.96%)	0.012*	23 (3.75%)	25 (8.16%)	M: 1.2 mg F: 1.1 mg	15 (4.9%)	0.101
Vitamin A	20-60 mcg/dL	147 (24.01%)	189 (61.76%)	M: 900 mcg F: 700 mcg	97 (31.69%)	< 0.00001*	158 (25.81%)	180 (58.82%)	M: 900 mcg F: 700 mcg	82 (26.79%)	< 0.00001*
Vitamin E	5.5-17 µg/mL	14 (2.28%)	100 (32.67%)	15 mg	59 (19.28%)	0.00016*	153 (25%)	97 (31.69%)	15 mg	43 (14.05%)	< 0.00001*
Vitamin C	0.6-2 mg/dL	128 (20.91%)	97 (31.69%)	45 mg	70 (22.87%)	0.014*	145 (23.69%)	94 (30.71%)	45 mg	67 (21.89%)	0.01314*
Vitamin D	20-40 ng/mL	172 (28.1%)	104 (33.98%)	15 mcg	41 (13.39%)	< 0.00001*	141 (23.03%)	150 (49.01%)	20 mcg	66 (21.56%)	< 0.00001*

*P-value significant at 0.05. ¹P-value for statistical analysis of variables between the two subgroups of patients who received supplements and patients who did not receive supplements in the younger than 45 years group. ²P-value for statistical analysis of variables between the two subgroups of patients who received supplements and patients who did not receive supplements in the older than 45 years group.

were not only better than in the group without a prescription for supplements postoperative, but also better than their evaluations preoperatively [Table 1]. Prevalent nutritional deficiencies in the group with a prescription for supplements were in vitamin A (31.69% for first group; 26.79% for second group; $P = 0.4354$), iron (27.77% for first group; 25.16% for second group; $P = 0.7489$), vitamin C (22.87% for first group; 21.89% for second group; $P = 0.7718$), and vitamin E (19.28% for first group; 14.05% for second group; $P = 0.08186$); the P -values for these variables in the groups of those younger and older than 45 years which received supplements mentioned above were not statistically significant. The analysis of the data revealed that the reduction of nutritional

deficiencies in some variables such as iron ($P = 0.00026$), biotin ($P < 0.00001$), zinc ($P < 0.00001$), vitamin B12 ($P = 0.018$), vitamin B1 ($P = 0.012$), vitamin A ($P < 0.00001$), vitamin E ($P = 0.00016$), vitamin C ($P = 0.014$), and vitamin D ($P < 0.00001$) was significant for patients younger than 45 years of age who received or did not receive supplements. In those older than 45 years, in addition to those variables, folic acid ($P = 0.0278$) and riboflavin ($P = 0.012$) were statistically significant among subjects with or without supplements [Table 1].

Relationship between hair loss and nutritional parameters

Subjects who complained of hair loss (effluvium or alopecia) were mostly postoperative women without a prescription for supplements (53% in the younger group; 58% in the older group), and in the older group without a prescription for supplements hair loss was also more frequent and statistically significant (82% in total) in comparison with the younger group without a prescription for supplements (69% in total) postoperatively ($P = 0.03236$) [Figure 1]. In the group with a prescription for supplements, the rate of hair loss was lower than in the group without a prescription for supplements (40% overall in the younger group; 36% overall in the older group) postoperatively [Figure 1]. The prevalence of hair loss regardless of age and gender among subjects with or without a prescription for supplements was significant at $P < 0.00001$.

DISCUSSION

After BS, many subjects complain of symptoms suggestive of nutritional deficiencies, the most frequently reported being hair loss, cramps, and paresthesia. Postoperative symptoms do not result in severe health consequences; they cause a daily discomfort for patients. Hair loss is a common complication after bariatric surgery and is reported in more than half of the subjects in the short term after BS. Hair loss is related to rapid weight reduction; furthermore, zinc, iron, and other micronutrient deficiencies can also be involved^[16,17]. There are only a few data on the treatment of these symptoms^[18]. Treatment of hair loss with vitamins B5 and B6 is common after BS, whereas there are no data on the association between hair loss after BS and deficits in these vitamins^[11]. This is the main reason for our study that aimed to determine the main deficiencies that underlie hair loss and their treatment with supplements after BS.

The frequently reported nutritional deficiencies after BS are iron, vitamin B12, vitamin D, vitamin B1, and zinc deficits^[10,11,20-23]. In our study, vitamin A, iron, and zinc deficits were the most frequently observed after BS. Indeed, we observed a higher prevalence of vitamin A, iron, and zinc deficits in both groups (those younger and older than 45 years of age) without a prescription for supplements compared to both groups with a prescription for supplements.

The analysis of patients with and without a prescription for supplements indicated significant differences for hair loss between the groups with and without hair loss concerning the postoperative use of supplements. The prevalence of hair loss was 69% and 82% in the younger and older groups, respectively, 12 months after BS, which is in line with previous reports^[24,25]. By using the supplements postoperatively, the prevalence of hair loss was only 40% and 36% in the younger and older groups, respectively.

Preoperative monitoring of the combination of several nutritional deficits could be used to identify patients at risk and prevent the onset of deficiencies and their consequences after BS^[26]. Identification and correction of micronutrient deficiencies was essential for treating hair loss. Our patients stated they benefited from supplements. Indeed, most patients stopped losing hair after being prescribed vitamin and mineral supplements one year after BS. As a consequence, diet counseling and adequate supplementation are required after BS to avoid hair loss. Postoperatively, all patients should receive lifelong supplementation.

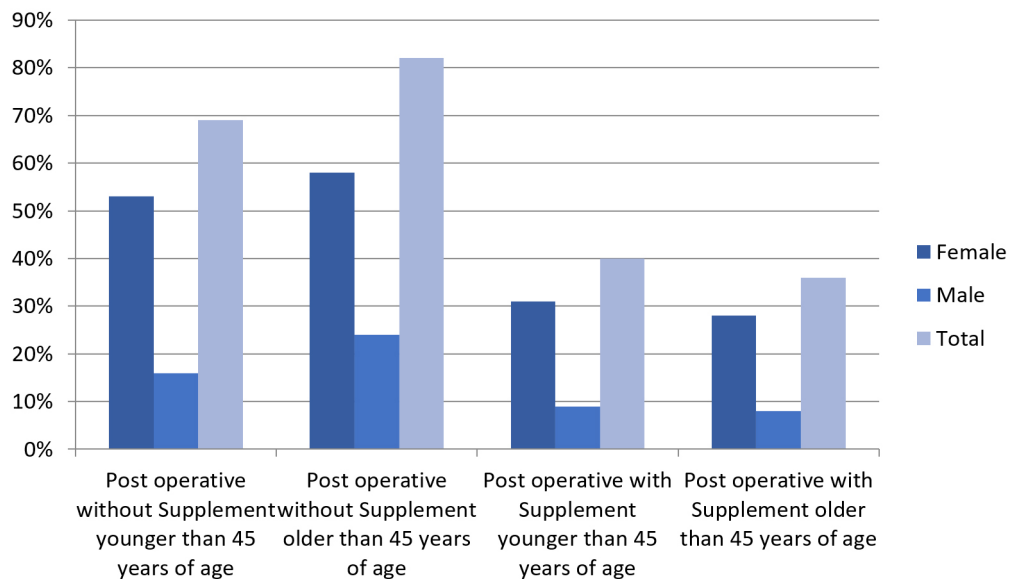


Figure 1. Prevalence of hair loss 12 months after bariatric surgery in those younger and older than 45 years of age, with or without a prescription for supplements. The prevalence of hair loss regardless of age and gender among subjects with or without a prescription for supplements was significant at $P < 0.00001$.

In conclusion, hair loss is a frequent postoperative complication after BS in morbidly obese individuals. Based on the results, the variable addition zinc + iron might be one of the predictors of hair loss, although further research is needed to demonstrate the correlation between preoperative status of nutritional deficiency and postoperative remission in bariatric subjects. Therefore, there is global need for monitoring nutrient status in these patients. Most of these deficiencies might be preventable and treatable with high-dose supplementation. With increased awareness of the potential nutritional consequences of BS, life-threatening complications related to nutritional deficits may be avoided.

DECLARATIONS

Authors' contributions

Study design: Anbara T, Kheirvari M

Data acquisition: Anbara T, Kheirvari M

Data analysis: Kheirvari M

Manuscript preparation: Kheirvari M

Supervision: Anbara T

Availability of data and materials

Readers can reach the data and materials through direct contact to authors' emails.

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Both authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Informed consent was obtained from all individual participants included in the study. The presented study

was approved by the Ethical Board of Erfan Niayesh Hospital.

Consent for publication

Informed consent was obtained from all individual participants included in the study. The presented study was approved by the Ethical Board of Erfan Niayesh Hospital.

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Review

Open Access



Review of intracorporeal and extracorporeal continent urinary diversion - where do we stand in 2021?

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Abstract

Robot-assisted radical cystectomy has become widely accepted as a safe and minimally invasive procedure for the treatment of bladder cancer. The urinary diversion continues to be performed completely intracorporeally or extracorporeally. Over the past decade, there has been an increasing number of continent diversions being performed intracorporeally. We evaluated the most recent literature regarding intraoperative metrics and outcomes that compare the intracorporeal and extracorporeal approaches.

Keywords: Cystectomy, intracorporeal, extracorporeal, continent urinary diversion

INTRODUCTION

Robot-assisted radical cystectomy (RARC) has become widely accepted as a safe minimally invasive procedure with equivalent oncologic outcomes^[1,2]. The RAZOR trial showed RARC to have similar progression-free survival to open radical cystectomy^[3]. Urinary diversion has historically been performed exclusively as an extracorporeal procedure, however, was first described using an intracorporeal technique in 2003 with the ileal conduit^[4]. Since then, it has gained increasing popularity with recent data showing up to 97% of diversions being performed intracorporeally within some groups^[5]. We aim to discuss the current



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status of intracorporeal and extracorporeal continent urinary diversion in the setting of RARC. We evaluate the most contemporary data examining operative and postoperative metrics used to assess intracorporeal and extracorporeal approaches to continent diversions.

EXTRACORPOREAL DEFINITION

The definition of an extracorporeal diversion varies among surgeons. For many, this means making a laparotomy incision and performing the entirety of the procedure open. For others, a more hybrid approach is used that involves making a much smaller 5-7 cm incision and utilizing the robot to perform the urethral and/or ureteral anastomoses. This difference cannot be under-emphasized, as the hybrid approach allows for the possibility of less ureteral mobilization as well as a more precise urethral anastomosis for the orthotopic diversions. While the literature does not readily differentiate between the two, we will herein assume they are all the same for the purpose of this discussion.

LEARNING CURVE

The learning curve associated with intracorporeal continent urinary diversion should not be understated. There have been estimations of the learning curve for RARC and the agreement of 21-30 cases for this specific procedure has been reached to accomplish a lymph node yield of 20 as well as a positive surgical margin rate of 5% or lower^[6]. While this may not seem like a large number of cases, “high volume centers” are 4-6 cases per year while “very high volume” centers are 7+ RARC/year^[7]. This means that for a surgeon transitioning to intracorporeal diversions, it could take many years to cover the 30 cases required for the extirpative portion of the surgery alone.

Some groups have attempted to overcome this by having a clear mentor and mentee set-up with a set number of cases required to be performed together before operating independently^[8]. In addition to this, some also have a group of nurses and technicians that exclusively work robotic cases and are present for all their diversion cases. While this would indeed aid with the learning curve, this is not feasible in all institutions.

OPERATIVE TIME

As we continue to move forward in the robotic era, the ever-pressing question continues to arise, “why should we continue to perform extracorporeal diversions over intracorporeal?” One of the big arguments is shorter operative times. Operative times from experienced surgeons range from 265-760 min^[9] for intracorporeal neobladders, while extracorporeal are 285-401^[10,11]. Even in the most experienced hands, 58%-64% of patients experience a complication within the first 90 days after radical cystectomy regardless of how the diversion is performed^[12,13].

Zhang *et al.*^[14] recently published their data of 948 patients with 26 months of follow-up looking at intracorporeal diversions *vs.* RARC and open diversion *vs.* open radical cystectomy with open diversion. They found that the open radical cystectomy with open diversion had the shortest operative time. This intuitively makes sense and continues to be a motivating factor towards open diversions to attempt to minimize the operative time of an already long procedure. Novara *et al.*^[13] found similar outcomes with shorter operative times associated with the open cystectomy. Shim *et al.*^[15] looked specifically at intracorporeal diversions compared to extracorporeal and found the operative time to also be significantly longer with the intracorporeal urinary diversion. Lenfant *et al.*^[10] also found that surgeons were less likely to offer a patient with an ASA score ≥ 3 an intracorporeal urinary diversion given the potentially longer exposure to Trendelenburg position with pneumoperitoneum. This difference cannot be ignored when comparing these two surgical approaches and must remain a continued part of the conversation.

In addition to longer operative times, performing extracorporeal diversions allows the surgeon to keep all diversion options available to patients. For example, if a surgeon is most comfortable with only the intracorporeal ileal conduit, they may be reticent to discuss a continent diversion option, orthotopic or cutaneous. This is critically important when discussing open and robotic diversions. Given the steep learning curve of robotic diversions, it is not unreasonable to think that many surgeons are prone to perform the procedure they are more comfortable and adept at rather than what may be best for the patient.

COMPLICATIONS

Ureteroenteric stricture formation

Stricture formation at the site of the anastomosis from the ureter to the bowel is a potentially catastrophic complication. These patients frequently require surgical intervention including invasive anastomotic revisions. Rates of ureteroenteric anastomotic stricture (UEAS) are reported to occur in 2.6%-13% of cases depending on the definition used^[16]. Goh *et al.*^[17] evaluated stricture formation between RARC and open radical cystectomy. They found that there was a higher stricture rate in the RARC group, however, this also related to the hospital volume, yet again emphasizing the steepness of the learning curve associated with these procedures. Of note, 84% of their diversions were incontinent diversions that were all performed extracorporeally.

Ericson *et al.*^[16] evaluated UEAS rates in open radical cystectomy, RARC with extracorporeal diversion, and RARC with intracorporeal diversion. Their cohort of an impressive 968 patients reported an overall 11.3% stricture rate. Their subsets were broken down to a 9%, 11.3%, and 13% rate for open, extracorporeal, and intracorporeal respectively with a statistically significant difference. What must be noted, however, is that the intracorporeal rate decreased from 17.5% to 4.9% after 75 cases; which again emphasizes the steep and long learning curve associated with these procedures. Also important to note in this cohort is that only 13% of their diversions were continent for the intracorporeal subset compared to 27% of their extracorporeal subset.

Ahmadi *et al.*^[18] looked at UEAS rates in intracorporeal diversions with and without the use of indocyanine green (ICG) for perfusion evaluation of the distal ureter. What they found was that not only was there a much greater amount of distal ureter excised before anastomosis (> 5 cm in some cases) but that the ICG group had a 0% stricture formation at 12 months of follow up compared to the 10.6% per patient rate in the non-ICG group. Shen *et al.*^[19] evaluated the stricture rate with extracorporeal diversions utilizing ICG with SPY fluorescence to evaluate for distal perfusion. They found the stricture rate again to be 0% in the ICG group *vs.* 7.5% in the non-ICG group. They also reported a longer excision of the distal ureter as well with 3.8 cm in the ICG group *vs.* 2.2 cm in the non-ICG group. These studies lead us to believe that perhaps the rate of UEAS is not dependent on the method of diversion creation, but rather distal ureteral perfusion^[19].

Gastrointestinal complications

Gastrointestinal complications continue to be a major cause of morbidity in the cystectomy patient. Patient's hospital stays are prolonged with ileus, jaundice, and hematochezia as well as readmissions for similar issues. Shim *et al.*^[15] looked at complications between intracorporeal urinary diversion and extracorporeal urinary diversion in 362 patients. They found that gastrointestinal complications were significantly higher in the extracorporeal urinary diversion group. Zhang *et al.*^[14] also found a significantly lower gastrointestinal complication rate with the intracorporeal urinary diversion compared to both the extracorporeal urinary diversion and the open cystectomy. They found that the TPN requirement was highest for open cases. Hussein *et al.*^[5], however, found no significant difference in gastrointestinal complications between the intracorporeal urinary diversion and extracorporeal urinary diversion group,

looking at 972 patients. Feng *et al.*^[20] found fewer gastrointestinal complications with intracorporeal urinary diversions with 60% being continent diversions. Ahmed *et al.*^[21] found that 10% of intracorporeal diversions had gastrointestinal complications compared to 23% of those who underwent extracorporeal diversion.

The lower gastrointestinal complication rates associated with intracorporeal diversions are thought to be due to less bowel manipulation, exposure and mobilization^[21]. Shim *et al.*^[15] defined gastrointestinal complications to include ileus, jaundice and hematochezia. Zhang *et al.*^[14] by contrast defined gastrointestinal complications as ileus, diarrhea, gastrointestinal bleeding, gastritis and/or *Clostridium difficile*. These subtle differences in inclusion criteria and definitions of what constitutes a gastrointestinal complication may begin to explain why these results are inconsistent across so many different studies.

POSTOPERATIVE PARAMETERS

Postoperative parameters including length of stay, infections, and overall complications are consistent metrics evaluated when discussing the benefits of robotic surgery. With ERAS protocols integrated into most systems now, the time to discharge has significantly decreased after large abdominal procedures including radical cystectomy^[22]. Hussein *et al.*^[5] evaluated intracorporeal vs. extracorporeal diversion after RARC outcome parameters in 972 patients and found that the intracorporeal diversion had more complications and readmissions, however, these were not high-grade complications. They also noted that there were more infectious complications associated with the intracorporeal diversions. There was also a 1 day longer admission with the intracorporeal diversion subset.

Shim *et al.*^[15] also examined the outcomes of intracorporeal urinary diversion vs. extracorporeal urinary diversion. They found that the intracorporeal urinary diversion group had significantly shorter recovery parameters including time to passage of flatus, the start of oral intake, and length of hospital stay. Mazzone *et al.*^[23] did not find any difference in length of stay between intracorporeal urinary diversion and extracorporeal urinary diversion. Lenfant *et al.*^[10] also found that there was no difference in length of stay between the two groups. The data regarding length of hospital stay remains highly variable and inconclusive. Tables 1 and 2 show intraoperative and post-operative parameters between intracorporeal and extracorporeal urinary diversions.

FUNCTIONAL OUTCOMES

There continues to be limited data on functional outcomes for intracorporeal urinary diversion. Functional outcomes are influenced by many factors including patient age, mental status, reservoir volume, and urethral length. Tyrirtzis *et al.*^[9] had a cohort of 70 patients with an 88% daytime continence rate with an orthotopic Studer neobladder performed intracorporeally. Of this group, 88.6% were men. At their one-year follow-up, 46 men and 2 out of 3 females were defined as the continent with < 1 pad per day. One of the females had hypercontinence requiring clean intermittent catheterization. Canda *et al.*^[29] reported daytime continence in 11 out of 17 patients who underwent intracorporeal urinary diversion with an orthotopic neobladder.

Obrecht *et al.*^[24] recently published their one-year data of intracorporeal orthotopic neobladder creation looking primarily at functional outcomes. They had a 100% “social continence” rate, defined as < 1 pad per day as well as post-void residual of 0 with a median pouch capacity of 404 cc^[24]. It is important to note, however, that this is a small sample of 12 patients that were all male. It is difficult to be able to extrapolate this data over larger, more diverse populations. In addition to this, continence definitions vary widely across studies with terms such as “daytime continence” and “social continence” sometimes being used interchangeably without having a consistent clear definition.

Table 1. Robotic radical cystectomy with intracorporeal urinary diversion operative and post-operative characteristics

Study	N	Length of surgery (min) (median/mean)	Length of stay (mean/median days)	Complication rate Clavien 1-2 90d/30d (%)	Complication rate Clavien 3-5 90d/30d (%)	GI complications (%)	Overall complication rate 90d/30d (%)	Continence (0-1 pad/d) (day %/night %)
Hussein <i>et al.</i> ^[11] 2020	486	355/-	-/9	-	14/12	23	52/47	-
Mazzone <i>et al.</i> ^[23] 2021	162	350/-	-/11.5	-	-/35.2	-	-	-
Lenfant <i>et al.</i> ^[10] 2018	74	320/-	-/14	6.7/38	12.2/9.5	-	18.9/47.3	-
Zhang <i>et al.</i> ^[14] 2020	301	390/-	6/-	-	16.9/10	23.3	44.2/37.5	-
Shim <i>et al.</i> ^[15] 2020	84	-/566	16.6/-	26.7/-	14.7	4.8	41.7/-	-
Obrecht <i>et al.</i> ^[24] 2020	12	575/-	-	-	-	-	-	100/75
Tyritzis <i>et al.</i> ^[9] 2013	70	420/-	-/9	17/-	37.1/-	21.4	51.2/48.4	68.5/57.4
Mistretta <i>et al.</i> ^[25] 2021	57	-	-	-	-	-	-	89.4/87.1
Balbay <i>et al.</i> ^[26] 2020	22	-/552	10.5/-	13.6/92	18.2/9	13.6	-	82.3/47.1
Tuderti <i>et al.</i> ^[27] 2020	167	420/-	-	-	-	-	-	70-90

Grimm *et al.*^[30], by contrast to the intracorporeal orthotopic neobladder, had 178 patients who underwent creation of orthotopic neobladder in an extracorporeal manner with 48.5% daytime continence and 34.9% nighttime continence. This group, however, does not specify which of these patients underwent RARC as opposed to open radical cystectomy^[30]. Mistretta *et al.*^[25] also compared continence rates of RARC with intracorporeal and extracorporeal orthotopic neobladders with no statistically significant difference in functional outcomes [Tables 1 and 2]. Lin *et al.*^[28] use a hybrid approach by performing a RARC, extracorporeal creation of the neobladder, and laparoscopic urethra-neobladder anastomosis with 90% daytime and 82% nighttime continence [Table 2]. Despite this, there is a paucity of data on the functional outcomes for extracorporeal urinary diversion after RARC, however, daytime rates in the larger open studies range from 54%-99% daytime continence 36%-84.6% nighttime continence^[12,31-35].

Limitations

Overall experience with intracorporeal and extracorporeal urinary diversion has grown immensely over the past 20 years. This report presents the most recent and robust studies to address the important questions to consider when deciding between the two techniques. While we can make see emerging themes within

Table 2. Robotic radical cystectomy with extracorporeal urinary diversion operative and post-operative characteristics

Study	N	Length of surgery (min) (median/mean)	Length of stay (mean/median days)	Complication rate Clavien 1-2 90d/30d (%)	Complication rate Clavien 3-5 90d/30d (%)	GI complications (%)	Overall complication rate 90d/30d (%)	Continence (0-1 pad/d) (day %/night %)
Hussein <i>et al.</i> ^[5] 2018	486	401/-	-/8	-	12/10	20	35/28	-
Mazzone <i>et al.</i> ^[23] 2021	105	350/-	-/13	-	-/42.9	-	-	-
Lenfant <i>et al.</i> ^[10] 2018	34	285/-	-/12	11.7/32.4	17.6/5.9	-	29.4/38.2	-
Zhang <i>et al.</i> ^[14] 2020	375	421/-	7/-	-	24.8/17.9	29.3	48.3/43.2	-
Shim <i>et al.</i> ^[15] 2020	278	-/510	22.4/-	41/-	20.5/-	12.9	61.5/-	-
Mistretta <i>et al.</i> ^[25] 2021	44	-	-	-	-	-	-	63.8/51.6
Lin <i>et al.</i> ^[28] 2008	108	-/330	-	-	-	-	18.5	90.7/82.6

this growing body of evidence, the paucity of level one evidence limits our ability to draw definitive conclusions.

CONCLUSIONS

RARC has taken over as the treatment of choice in most cases in the treatment of muscle-invasive bladder cancer. As intracorporeal urinary diversion continues to gain popularity, we need to continue to challenge the data and evaluate if we are making the right decision for our patients. After looking across the data provided worldwide, there continues to be a reason to pause with the sweeping adoption of the intracorporeal urinary diversion with continued varied data of the superiority of outcomes.

DECLARATIONS

Authors' contributions

Balzano FL and Chan KG contributed equally to all components of the manuscript.

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Conflicts of interest

Both authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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Systematic Review

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Surgical and functional outcomes after robot-assisted radical cystectomy in female patients: a systematic review of the literature

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Abstract

Aim: We aimed to review and summarize recent data on surgical and functional outcomes in women undergoing robot-assisted radical cystectomy (RARC) and urinary diversion (UD) for bladder cancer, compared with male and open counterparts.

Methods: A systematic review of English-language articles published in the last 15 years was performed on PubMed/Medline database according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Outcomes of interest included peri- and post-operative surgical outcomes [operative time (OT), estimated blood loss (EBL), hospital stay (LOS), complications, and readmission], pathological outcomes [pT stage, lymph node (LN) yield, positive surgical margins (PSMs), and positive LN (pN+)], and functional outcomes [daytime and nighttime continence, sexual activity, need for clean intermittent catheterization (CIC), and quality of life (QoL) evaluation].

Results: Overall, eight studies were selected collecting data from 229 female patients undergoing RARC. The median OT was 418 min (range 311-562 min) and the median EBL was 380 mL (range 100-1160 mL). OT and EBL were not significantly different comparing males and females, whereas the robotic approach was found to be



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significantly related with longer OT and lower EBL compared to the open procedure. The median LOS was 9.8 days (range 6.5-21 days); no significant differences in LOS were found between open RC (ORC) and RARC in female patients, as well as between RARC in women and men. The mean incidence of 30-day complications after RARC in women was 32.9%, with 12% of high-grade complications, while the 30- and 90-day readmission rates were 20.8%, and 28%, respectively. Complications and readmission comparing RARC and ORC in female patients appear to be overlapping. The mean rate of PSMs was 2.5% and the mean rate of pN+ was 12.7%; both these outcomes were similar in RARC compared with ORC. The mean number of retrieved LN was 20.6 (range 11.3-35.5). The LN yield resulted significantly influenced by the robotic approach [median 27 (range 19-41)] compared to the open one [20.5 (range 13-28)]. After 12 months, the rate of women with daytime and nighttime continence was 66.7%-90.9% and 66.7%-86.4%, respectively, while that of sexually active women ranged 66.7%-72.7%. The need for CIC ranged 12.5%-27.2%. Administering the EORTC-QLQ-C30 questionnaire after RARC and intracorporeal neobladder, the global health status/QoL and physical and emotional functioning items improved significantly over time.

Conclusion: RARC and UD in female patients is a feasible procedure with surgical outcomes overlapping with those in the male patient population. Postoperative functional outcomes on continence, sexual function, and QoL are still poorly investigated, although results inherent in the nerve-sparing approach appear promising.

Keywords: Bladder cancer, robot-assisted radical cystectomy, female, surgical outcomes, functional outcomes

INTRODUCTION

Bladder cancer (BCa) is the second most common genitourinary malignancy, with 81,400 new cases and 17,980 deaths estimated in 2020 in the United States^[1]. Although BCa is more frequent among men, among women there are approximately 20,000 new cases and about 5000 women die each year from this disease^[1].

Radical cystectomy (RC) with urinary diversion (UD) is considered the standard treatment for non-metastatic muscle-invasive bladder cancer and high-risk non-muscle-invasive bladder cancer^[2,3]. Women present an advanced stage at diagnosis more often, increasing the requirement of RC^[4,5]. In female patients, the standard surgical procedure is represented by anterior pelvic exenteration including the removal of the bladder, ovaries, uterus, and anterior vaginal wall^[2]. RC, whether open (ORC) or robot-assisted (RARC), is a morbid and complex procedure that involves simultaneous surgeries on the urinary and gastrointestinal tracts, as well as the retroperitoneum, with a substantial complication rate that may increase the length of hospital stay (LOS) and readmissions^[6]. The robotic approach is increasingly performed worldwide^[7]. Reportedly, progress in robotics has helped to develop standardized mini-invasive procedures which seem to offer oncological outcomes similar to open procedures and that are associated with reduced peri- and post-operative morbidity (decreased postoperative pain, incisional morbidity, blood loss, and transfusion rate) and shorter LOS, with an earlier return of bowel function^[8-10]. After performing RARC, ileal conduit remains the most common type of reconstruction, even though an orthotopic neobladder (ONB) could offer a better quality of life (QoL) by maintaining body image and normal voiding in suitable patients^[11].

According to a recent review on gender-differentiated oncological and functional outcomes after RC, being a woman negatively affects oncologic outcome secondary to delays in diagnosis, treatment, and misdiagnosis. Moreover, functional outcomes (urinary, sexual, and overall QoL) are poorly assessed in women using non-validated and non-standardized measures^[5]. Recent frontiers of improvement seem to be offered by totally intracorporeal reconstruction [intracorporeal urinary diversion (ICUD)] vs. extracorporeal UD (ECUD)^[12] and the nerve-sparing (NS)-RARC^[13]. However, data on postoperative outcomes in female patients are still scarce and confusing, especially concerning the robotic approach.

This systematic review aimed to comprehensively summarize the current evidence in the literature on surgical and functional outcomes after RARC in female patients, to identify the gaps and direct future investigations.

METHODS

Literature search strategy and study selection

A systematic review of the English-language literature published in the last 15 years (from 1 January 2005 to 31 December 2020) was performed. The US National Institutes of Health's PubMed Database was carefully scrutinized according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement^[14]. The research was performed using the following search string: [*radical cystectomy AND robot AND female AND (surgical outcome OR functional outcome)*]. According to the aim of this study, all eligible texts reporting the peri- and post-operative outcomes under examination in female patients treated with RARC for BCa were included in the systematic review. After a first screening based on study title and abstract, all articles were examined based on full-text and excluded with reasons when inappropriate. The following types of articles were excluded from the systematic review: review articles, case reports, editorial/author replies or comments to other articles, studies reporting data without gender differentiation, studies from the same database with potential overlapping patients, and studies that dealt with research unrelated to our topic.

Outcomes of interest

Our primary outcomes were peri- and post-operative surgical outcomes [operative time (OT), estimated blood loss (EBL), LOS, 30- and 90-day complication rates according to Clavien-Dindo Classification System (CCS)^[15], and 30- and 90-day readmission rates] and postoperative functional outcome [daytime and nighttime continence, sexual activity, need for clean intermittent catheterization (CIC), and health-related QoL (HRQoL) evaluation]. As secondary endpoints, we considered postoperative pathological outcomes [pT stage, lymph node (LN) yield, positive surgical margins (PSMs), and positive LN (pN+)].

RESULTS

Evidence synthesis

Figure 1 reports the flow diagram of the selection process used for this systematic review. From a total of 296 articles screened, 17 were initially assessed for eligibility. Of these, 9 were subsequently excluded after full-text evaluation and eight were selected and critically analyzed by the authors.

Study population and design

Overall, our systematic review included 514 patients (438 considering RARC only). Regarding the articles which included both male and female patients, given the topic of our systematic review, we focused particularly on female patients, in total 305 (229 considering RARC only). The characteristics of the eight identified studies together with the peri- and post-operative outcomes achieved are reported in **Table 1**.

Eligible articles were published between 2009 and 2020 involving female patients who underwent RARC from December 2003 to June 2018. All selected studies had a retrospective design; only one was a multicenter study^[16], whereas all others were based on data collected in a single institution. Four of the eight studies were from the USA^[17-20], one from Turkey^[21], one from Sweden^[22], one from Italy^[13], and one from Korea^[16]. Three of them were comparative articles: two reported gender comparison data^[16,19] and one compared RARC and ORC^[18].

Table 1. Overview of the studies investigating surgical and functional outcomes in female patients with bladder cancer treated with robot-assisted radical cystectomy, grouped by endpoints of interest

Author, year	Study design	Study size	Type of surgery	Follow-up	Type of urinary diversion	Preoperative variables	Peri- and Post-operative outcomes	Findings
Tuderti <i>et al.</i> ^[13] , 2020	Retrospective (monocentric study)	11	SS-RARC	Median of 28 months (IQR 14-51)	iN	Age, BMI, gender, ASA score, preoperative eGFR, preoperative Hb, NAC rate	<ul style="list-style-type: none"> - Surgical: OT, Hb at discharge, LOS, complications according to CCS; - Pathological: pT stage, pN stage, histology, LN yield, PSMs; - Oncological: 1-year RFS, 1-year CSS, 1-year OS; - Functional: last eGFR, ONB stones, UES, need for CIC; daytime and nighttime continence, recovery probabilities; EORTC QLQ-C30 and EORTC QLQ-BLM30; FSFI questionnaire 	<p>Median OT was 255 min and the median LOS 7 days. Low-grade CCS complications occurred in 4 patients (36.3%), while high-grade CCS not observed. 7 patients (63.7%) had an organ-confined disease at the pathologic specimen; nodal involvement and PSMs not detected</p> <p>No new onset of CKD stage 3b. After one year, daytime and nighttime continence rates were 90.9% and 86.4%, respectively. Three patients (27,2%) performed CIC twice a day</p> <p>QoL as well as physical and emotional functioning (EORTC QLQ-C30) improved significantly over time (all $P \leq 0.04$), while urinary symptoms (EORTC QLQ-BLM30) and sexual function (FSFI) worsened at 3 months with a significant recovery taking place at one year (all $P \leq 0.04$)</p> <p>Overall, 8 out of 11 patients (72.7%) were sexually active at the 12-month evaluation</p>
Narayan <i>et al.</i> ^[18] , 2019	Retrospective (monocentric study)	122	ORC (76), RARC (46)	NR	ICUD (40/46 RARC); ECUD	Age, race, BMI, smoking, NAC, ASA score, CCI, prior pelvic surgery, preoperative TNM	<ul style="list-style-type: none"> - Surgical: OT; EBL, IT, PT, ICU, LOS, 30- and 90-day complication rates according to CCS, 30- and 90-day readmission rates; - Pathological: pT stage, pN stage, pM stage, LVI, LN yield, PSMs 	<p>LOS ($P = 0.13$) was not statistically different between the groups</p> <p>OT was longer for RARC compared with ORC [median 513 min (IQR 365-810) vs. 392 (IQR 208-875), respectively, $P < 0.001$]</p> <p>ORC women were significantly more likely to require an IT: OR for ≥ 1 unit during ORC was 9.97 (95%CI: 3.39-29.31, $P < 0.001$) on multivariable analysis. Nearly 68% of ORC women received an IT, compared with only 24% of RARC women. EBL was also significantly greater in ORC group: median of 762 mL (IQR 600) compared to 275 mL (IQR 350 mL) among RARC ($P < 0.01$). PT were not different between the 2 groups (36% ORC vs. 26% RARC, $P = 0.32$). Considering IT and PT together, ORC women were significantly more likely to have undergone transfusion of ≥ 4 units compared to RARC women with a OR 21.06 (95%CI: 6.51-68.44, $P < 0.001$) on multivariable analysis</p> <p>PSMs rate was low overall (4.9%), with no statistically significant difference between the 2 techniques (4 for ORC and 2 for RARC)</p>

								LN yield was higher for RARC compared with ORC, with a median of 27 nodes (IQR 7-57) compared with 20.5 nodes (IQR 0-57) ($P < 0.001$). The overall rate of N+ disease was low between both groups ($P = 0.89$) The overall complication rate was 75.4%, with no difference in rates between groups (76.3% vs. 73.9%, respectively, $P = 0.83$) The majority of complications (89.5% vs. 82.3%) were < 3 CCS complications Overall 30- and 90-day readmission rates were 24% and 29.8%, respectively, with no difference observed between ORC or RARC groups ($P = 0.67$ and $P = 0.68$)
Whittum <i>et al.</i> ^[17] , 2018	Retrospective (monocentric study)	118	RARC	Median of 9 months (IQR 6-13) for organ invasion; 23 months (IQR 8-45) for no organ invasion	IC (106); others (12)	Age, BMI, ASA score, NAC, prior abdominal/pelvic surgery, prior RT, LVI at TURBT, tumor site at TURBT, histology at TURBT	- Surgical: OT, type of UD, EBL, ICU, LOS, 30- and 90-day complications, 30- and 90-day readmission; - Pathological: pT stage (gynecological organ invasion), pN stage, histology, PSMs; - Oncological: AC; 30- and 90-day OS	17 patients (14%) showed a gynecological organ invasion at pathological specimen. These patients had more LVI at TURBT (82% vs. 46%, $P = 0.006$), trigonal tumours at TURBT (59% vs. 18%, $P = 0.001$), multifocal disease (65% vs. 33%, $P = 0.01$), (71% vs. 22%, $P < 0.001$), PSMs (24% vs. 4%; $P = 0.02$), and they less commonly demonstrated pure urothelial carcinoma at TURBT (18% vs. 66%, $P < 0.001$) There was no statistically significant difference between the two groups in terms of hospital or ICU stay, complications, readmissions, mortality at 30 and 90 days On multivariate analysis, significant predictors of gynecological organ invasion were pN positive disease (OR 6.48, 95%CI: 1.64-25.51, $P = 0.008$), trigonal tumour location (OR 5.72, 95% CI: 1.39-23.61, $P = 0.02$), and presence of variant histology (OR 18.52, 95%CI: 3.32-103.4, $P = 0.001$)
Tyritzis <i>et al.</i> ^[22] , 2013	Retrospective (monocentric study)	70 (62 male, 8 female)	RARC (nerve sparing-RARC in all female)	Median of 30.3 months (IQR 12.7-35.6)	iN	Age, sex, BMI, ASA score, preoperative TNM, preoperative grade, concomitant CIS, NAC.	- Surgical: OT, type of PLND, nerve sparing, EBL, LOS, ≥ 30 -day/90-day complications according to CCS; - Pathological: pT stage, pN stage, concomitant CIS, PSMs, GS, LN yield; - Oncological: 24-month recurrence, recurrence location, RFS, CCS, OS; - Functional: 6/12-month daytime and nighttime continence (≤ 1 pad/die), 6/12-month potency and	They recorded negative margins in 69 of 70 patients (98.6%). Clavien 3-5 complications occurred in 22/70 patients (31.4%) at 30-day and 13/70 (18.6%) at > 30 -day. At 90-day, the overall complication rate was 58.5%. Clavien < 3 and Clavien ≥ 3 complications were recorded in 15/70 patients (21.4%) and 26/70 (37.1%), respectively Kaplan-Meier estimates for RFS, CSS and OS at 24 months were 80.7%, 88.9%, and 88.9%, respectively Daytime and nighttime continence at 12 months reaches 80%-90% in men and 70% women. At 12 months, 46 men (74.2%) and 2 of 3 evaluable females (66.7%) were continent. One female

							sexual activity	patient had to perform CIC (12.5%). 26 (81.2%) of the nerve-spared patients were potent with or without PDE5-I at 12 months. 4 of 6 evaluable women (66.7%) remained sexually active postoperatively. Preoperatively potent patients remained sexually active after surgery. Age will have a negative impact on outcomes in preserving daytime continence and in achieving successful sexual function
Kaufmann <i>et al.</i> ^[20] , 2011	Retrospective (monocentric study)	12	RARC	Median of 9.0 ± 6.0 months	IC (10); ONB (1); IP (1)	Age, BMI	- Surgical: OT, type of UD, EBL, TTF, LOS, complications; - Pathological: pT stage, pN stage, LN yield, PSMs, histology	Median total OT was 6.4 ± 1.5 h. Median EBL was 275.0 ± 165.8 mL. Median TTF was 3.5 ± 1.4 days. Median LOS was 8.0 ± 1.6 days. 4 patients were T2N0 or less, 5 patients T3N0, 1 patient T3N1 and 2 patients T4N0. There was one PSM in a patient with stage pT4aNO disease. Median LN yield removed was 23 ± 11.4. 1 had a recurrent ureteroenteric stricture, 1 had colpocleisis for vault prolapse, and 3 had metastatic disease
Canda <i>et al.</i> ^[21] , 2011	Retrospective (monocentric study)	27 (25 male, 2 female)	Nerve sparing-RARC	Mean of 6.3 months (IQR 1.8-11.3)	IC (2); iN (2 female/25)	Age, sex, BMI, preoperative IIEF score, preoperative TNM, CCI, ASA score, prior abdominal surgery, smoking, mean creatinine level	- Surgical: OT, type of PLND, nerve sparing, EBL, LOS, 30-day/90-day complications according to CCS, readmission; - Pathological: pT stage, pN stage, PSMs, GS, LN yield; - Functional: daytime [none (0-1 pad/die), mild (1-2 pads/die), moderate (3 pads/die) and severe (> 3 pads/die)] and nighttime [good (dry, no protection), fair (dry, one awakening) and poor (wet, leakage and incontinence during sleep)] continence, postoperative IIEF	The mean OT, EBL and LN yield were 9.9 (IQR 7.1-12.4) h, 429 (IQR 100-1200) mL and 24.8 (IQR 8-46), respectively. The mean LOS was 10.5 (IQR 7-36) days, there was one perioperative death (3.7%), surgical margins were negative in all but one patient who had pT4b disease Pathological stages: pT0 (5), pTis (1), pT1 (1), pT2a (5), pT2b (3), pT3a (6), pT3b (2), pT4a (3) and pT4b (1). N + and incidental prostate cancer were detected in 6 and 9 patients, 3 patients died from metastatic disease and 1 from cardiac disease Complications: there were 9 minor and 4 major 30-day complications; 4 minor and 3 major 90-day complications (31-90 days) Of the available 18 patients, 11 were fully continent, four had mild and two had severe daytime incontinence. Concerning two female patients who underwent intracorporeal Studer pouch, both currently have severe (> 3 pads/die) daytime and poor (wet, leakage and incontinence during sleep) nighttime urinary incontinence. However, the postoperative follow-up is very limited for these 2 patients (6 and 5 months)
Kang <i>et al.</i> ^[16] , 2010	Retrospective (multicenter study)	104 (82 male, 22 female)	RARC	Mean of 12 months (IQR 3-24)	IC (13 female/60); ONB (9)	Age, sex, BMI, preoperative TNM, ASA score,	- Surgical: OT, EBL, IT, type of PLND, type of UD, TTF, LOS, complications	The mean total OT was 554 min (567 in female, 550 in male, $P = 0.64$), and the mean EBL was 526 mL (591 in female, 515 in male, $P = 0.32$)

				female/44)			according to CCS; - Pathological: pT stage, pN stage, PSMs, LN yield, histology; - Oncological: DFS	The TTF and bowel movement was about 3 days ($P = 0.38$), and LOS was about 18 days (20 in female, 17.7 in male, $P = 0.19$) The mean LN yield removed were 18 (16.0 in female, 19.1 in male, $P = 0.32$), and 10 patients had node metastatic disease on final pathologic evaluation. Postoperative complications occurred in 28 (26.9%) patients, major complications in 8 (7.7%) patients, and minor complications in 20 (19.2%) patients
Pruthi et al. ^[19] , 2009	Retrospective (monocentric study)	50 (40 male, 10 female)	RARC	Median of 14 months (IQR 0.2-73)	IC (7 female/30); ONB (3 female/20)	Age, sex, BMI, preoperative TNM	- Surgical: OT, type of UD, EBL, TTF, LOS, 30-day complications; - Pathological: pT stage, pN stage, PSMs, LN yield	Female patients had shorter OT (4.6 h vs. 5.9 h, $P < 0.001$), less EBL (215 mL vs. 330 mL, $P = 0.012$) and approached a shorter time to bowel movement (2.4 days vs. 2.8 days, $P = 0.057$). Mean TTF was 1.9 days (vs. 2.2 days), and mean LOS was 4.9 days vs. 4.4 days). These outcomes were comparable to the male patients, particularly the 20 male patients undergoing RARC during the same time period On surgical pathology, 5 patients were \leq pT2 (vs. 28), 3 patients pT3 (vs. 6), and 2 patients N+ (s 6). There were no PSMs. Mean number of LN removed was 19 (IQR 12-34), vs. 18 (IQR 8-37). Males were more often organ confined in our series (70% vs. 50%), but node-positive rates were not significantly different (15% vs. 20%) In female patients, 30-day complications included 2 complications in 2 patients. Complication rates in the male cohort was 30%, but this was not found to be statistically different than the rate in females

RC: Radical cystectomy; RARC: robot-assisted radical cystectomy; SS-RARC: sex-sparing-robot-assisted radical cystectomy; ORC: open radical cystectomy; LRC: laparoscopic radical cystectomy; IQR: interquartile range; iN: intracorporeal neobladder; BMI: body mass index; ASA: American society of anesthesiologists; OT: operative time; Hb: hemoglobin; LOS: length of hospital stay; CCS: Clavien-Dindo classification system; AC: adjuvant chemotherapy; NAC: neoadjuvant chemotherapy; PSMs: positive surgical margins; UES: uretero-enteric strictures; CIC: clean intermittent catheterization; FSFI: female sexual function index; CKD: chronic kidney disease; QoL: quality of life; NR: not reported; UD: urinary diversion; ICUD: intracorporeal urinary diversion; ECUD: extracorporeal urinary diversion; CCI: Charlson comorbidity index; EBL: estimated blood loss; IT: intraoperative transfusion; PT: postoperative transfusion; OR: odds ratio; CI: confidence interval; LN: lymph node; ONB: orthotopic neobladder; IC: ileal conduit; CCD: continent cutaneous diversion; IPC: Indiana pouch; RFS: recurrence-free survival; OS: overall survival; DFS: disease-free survival; UTI: urinary tract infection; RT: radiotherapy; ICU: intensive care unit; LVI: lymphovascular invasion; TURBT: transurethral resection of bladder tumour; TTF: time to flatus; OS: overall survival; CSS: cancer-specific survival; CIS: cancer in situ; GS: Gleason Score; PLND: pelvic lymph node dissection; IIEF: international index of erectile function; PDE5-I: phosphodiesterase type 5 inhibitors.

All articles collected dealt with female patients undergoing RARC. In three of these studies, the technique applied was NS^[13,21,22], specifically to safeguard functional postoperative outcomes. One article also included ORC, comparing the outcomes of the two approaches^[18].

The female patients underwent different types of UD: most of them underwent ileal conduit (136 cases), while 34 underwent neobladder; in 13 cases, it was defined as ONB and in 21 cases it was defined as intracorporeal neobladder (iN). One patient underwent Indiana pouch, while in 58 cases the type of urinary reconstruction was not specified.

Preoperative characteristics

The mean age of the female patients was 61.12 years (range 48.25-71.25 years). The mean body mass index (BMI) recorded was 24.7 kg/m² (range 19.8-34 kg/m²). Three of the studies also reported the preoperative ASA (American Society of Anesthesiologists) score^[13,17,18]. In the study by Narayan *et al.*^[18], comparing RARC and ORC, the rate of patients with ASA ≥ 3 was high and similar in RARC vs. ORC (93.48% vs. 92.11%, $P = 1$). In contrast, the study by Tuderti *et al.*^[13], which focused on sex-sparing (SS)-RARC, enrolled patients with a low ASA score (< 3) in more than 90% of cases. Whittum *et al.*^[17] found that a higher percentage of patients with an ASA score ≥ 3 was associated with gynecological organ invasion at RARC histology, although this did not reach statistical significance (76% vs. 57%, $P = 0.14$).

Peri- and post-operative surgical outcomes

The median OT of RARC in female patients was 418 min (range 311-562 min). The median EBL was 380 mL (range 100-1160 mL). Pruthi *et al.*^[19], when comparing female and male patients, reported that women had shorter OT (mean 276 min vs. 354 min, $P < 0.001$) and less EBL (mean 215 mL vs. 330 mL, $P = 0.012$). This difference was only significant, however, comparing female patients with a cohort of 20 male patients operated at the beginning of the learning curve, whereas no parameters were different between the female and the concurrent male patients. Kang *et al.*^[16] also compared perioperative outcomes between females and males. They obtained non-significant differences in OT (median 567 min vs. 550 min, $P = 0.64$) and EBL (median 591 mL vs. 515 mL, $P = 0.32$).

In the study by Narayan *et al.*^[18], OT was longer for RARC compared with ORC [median 513 (IQR 365-810) min vs. 392 (IQR 208-875) min, respectively, $P < 0.001$], and the median EBL in RARC was significantly lower than in ORC [275 (IQR 150-700) mL vs. 762 (IQR 100-7000) mL, $P < 0.01$]. Furthermore, women who underwent ORC were significantly more likely to require an IT. OR for the transfusion of ≥ 1 unit during ORC was 9.97 (95%CI: 3.39-29.31, $P < 0.001$) on multivariable analysis: nearly 68% of women who underwent ORC received an IT, compared with only 24% of those that underwent RARC. EBL was also significantly greater in the ORC group: median of 762 mL (IQR 600 mL) compared to 275 mL (IQR 350 mL) in the RARC group ($P < 0.01$). Postoperative transfusion (PT) did not differ between the two groups (36% ORC vs. 26% RARC, $P = 0.32$). Considering IT and PT together, women who underwent ORC were significantly more likely to have undergone the transfusion of ≥ 4 units compared to RARC with a OR 21.06 (95%CI: 6.51-68.44, $P < 0.001$) on multivariable analysis.

The median LOS was 9.8 days (range 6.5-21 days) with a median time to flatus (TTF) of 3.5 days. Postoperative LOS did not seem to be significantly influenced by the type of surgical approach [ORC vs. RARC: median 6 (IQR 5-8) days vs. 5 (IQR 4-7) days, $P = 0.13$]^[18]. No differences were found when comparing female to male RARC patients in the studies by both Pruthi *et al.*^[19] (mean 4.9 days vs. 4.4 days, $P > 0.05$) and Kang *et al.*^[16] (median 20 days vs. 17.7 days, $P = 0.19$).

All included studies reported the complication rate. The mean incidence of early postoperative complications (30-day complications) was 32.9%, with a percentage of high-grade complications (CCS ≥ 3) that tended to be low, averaging around 12%. Narayan *et al.*^[18] found no difference in rates of overall complications between ORC and RARC groups (76.3% vs. 73.9%, respectively, $P = 0.83$). Although the complication rate was higher in this study compared to the others, most of them (89.5% for ORC and 82.3%

for RARC) were < 3 CCS complications. Whittum *et al.*^[17] recorded complication rates within 30 and 90 days after surgery in their study, which were 49% and 61%, respectively. Furthermore, when comparing patients with gynecological organ invasion at RC histology with those without, there was no significant difference between the two groups in the rate of postoperative complications (30-day: 47% vs. 51%, $P = 0.79$; 90-day: 59% vs. 62%, $P = 0.78$).

In the studies collected in our research, the readmission rate after RARC in women was 20.8% in the first 30 postoperative days and 28% in the first 90 days. Narayan *et al.*^[18] showed that these rates were overlapping with ORC (ORC vs. RARC, 30-day: 22.67% vs. 29.09%, $P = 0.67$; 90-day: 28% vs. 32.61%, $P = 0.68$).

Postoperative pathological outcomes

The average detection rate of pT3 on histological examination of RARC was about 33%, with similar rates compared to the open approach^[18].

Surgical margins were negative in close to 100% of operations (with a mean of 97.5%). The robotic approach was similar to the open approach (PSMs 4.44% vs. 5.26%, $P = 1$)^[18]. The association between PSMs and gynecological organ invasion was significant (24% of cases vs. 4% of cases without invasion, $P = 0.02$)^[17]. In the multivariable analysis performed by Whittum *et al.*^[17], the number of pN+ (OR = 6.48, 95%CI: 1.64-25.51, $P = 0.008$), the trigonal tumor location (OR = 5.72, 95%CI: 1.39-23.61, $P = 0.02$), and the presence of variant histology other than pure urothelial (OR = 18.52, 95%CI: 3.32-103.4, $P = 0.001$) were confirmed as predictors of gynecological organ invasion.

In the cohort of female patients undergoing RARC collected in our study, the mean pN+ rate was 12.72%. The difference with the rate of pN+ found after ORC did not reach statistical significance ($P = 0.89$)^[18].

The mean number of retrieved LN (LN yield) was 20.6 (range 11.3-35.5). The number of total LN removed was significantly influenced by the robotic approach compared to the open one: in the study by Narayan *et al.*^[18], the median LN yield resulted 27 (IQR 19-41) for RARC and 20.5 (IQR 13-28) for ORC ($P < 0.001$). The difference between female and male cohorts was not statistically significant: mean LN removed 19 (range 12-34) vs. 18 (8-37) in the study by Pruthi *et al.*^[19] and 16 vs. 19 ($P = 0.32$) in the study by Kang *et al.*^[16].

Postoperative functional outcomes

Three of the collected studies reported data on recovery of urinary continence and sexual function after RARC in iN female patients. One of these also administered a questionnaire to assess HRQoL^[13].

The study by Canda *et al.*^[21], collecting the initial experience of NS-RARC in their institute, described poor functional outcomes in the only two female patients who underwent the procedure (NS-RARC and intracorporeal Studer pouch): at the time of data collection, they both had severe (> 3 pads/die) daytime and poor (wet, leakage, and urinary incontinence (UI) during sleep) nighttime UI. However, the postoperative follow-up was very limited for these two patients (6 and 5 months).

The study by Tyritzis *et al.*^[22], analyzing the effects of RARC on both male and female patients (all female patients received a NS procedure by preserving the autonomic nerves identified on the anterior vaginal wall at the 10 o'clock and 2 o'clock positions), showed the continence rate for daytime and nighttime at 12 months of follow-up was 74.2% for men, while two out of three evaluable female patients (66.7%) were continent (≤ 1 pad/die) during both daytime and nighttime. No need for a pad was recorded in 27.5% of

men (27.5%) and one woman (12.5%). One female patient had to perform CIC (12.5%). Four of six evaluable women (66.7%) remained sexually active postoperatively; among men, 26 (81.2%) of the nerve-spared patients were potent with or without PDE5 medication at 12 months.

Finally, the study by Tuderti *et al.*^[13], the most recent study included in our research, aimed to illustrate the results of the SS-RARC technique (with the preservation of utero-vaginal hypogastric plexus) in women receiving iN. In their cohort of patients, daytime and nighttime continence recovery probabilities after one year of follow-up were 90.9% and 86.4%, respectively. Three patients had to perform CIC twice a day (27.2%). Concerning the EORTC-QLQ-C30 questionnaire, global health status/QoL and physical and emotional functioning items improved significantly over time (all $P \leq 0.04$). According to the EORTC-QLQ-BLM30 questionnaire, specific for BCa, urinary symptoms worsened at 3 months with a significant recovery at one year ($P = 0.02$). The Female Sexual Function Index (FSFI) global score and FSFI domains such as arousal, lubrication, orgasm, satisfaction, and pain worsened over the first 3 months with a subsequent improvement at one year (all $P \leq 0.04$). Moreover, comparing baseline *vs.* one-year scores, arousal and orgasm domains experienced a complete recovery (both $P = 0.10$), while lubrication, satisfaction, and pain domains, as well as FSFI global scores, experienced a satisfying improvement but were statistically significantly lower than baseline (all $P \leq 0.025$). Overall, 8 out of 11 patients (72.7%) were sexually active at the 12-month evaluation.

As supplementary analysis, the authors compared a cohort of standard RARC patients with the SS-RARC cohort. The two cohorts were homogeneous for all baseline, clinical, and pathological features (all $P \geq 0.14$) except for age, with SS-patients being significantly younger (47.1 years *vs.* 61.7 years, $P < 0.001$). Perioperative complications and LOS were comparable between the groups ($P = 0.25$ and $P = 0.67$, respectively). Daytime continence recovery probability was significantly higher in the SS-cohort (one-year rate 90.9% *vs.* 74%, log-rank $P = 0.02$).

DISCUSSION

The treatment of BCa in female patients has historically been challenging for specialists, not only because of the possibility of a mismatch among surgical, oncological, and QoL outcomes due to the complexity of the procedure and the patient herself but also because the female gender represents a risk factor for poor surgical and oncological results after RC^[23]. Regarding surgical and functional outcomes (urinary function, sexual function, and HRQoL), the literature on RC in female patients, as reported in a recent review by Sadighian *et al.*^[5], is still sparse and poorly defined because of the exclusion of women from most studies, small sample sizes, various surgical techniques, and lack of validated questionnaires and standard definitions. Furthermore, the available evidence in the literature on RARC, particularly in female patients, is still relatively recent and scarce, and the data come mainly from small retrospective series. The robotic approach itself is described as less used in female BCa patients than the open approach in several studies^[24-29], although in others the difference was not statistically significant^[30-34]. It should be noted, however, that numerous articles comparing the use of ICUD *vs.* ECUD found no significant difference in the use of the two reconstructive approaches according to gender^[35-37], with even a prevalence of ICUD in female patients^[38].

The reviewed evidence suggests that the mean age of female patients undergoing RARC was 61.12 years. They were generally patients with a normal BMI (24.7 kg/m²). The median OT was 418 min. From our results, the duration of RARC in women resulted comparable with that in men, while the difference in duration between robotic and open approaches was significant^[18]. However, ORC was found to be a procedure with a higher risk of IT compared to RARC^[18]. Regarding LOS, the median time in our study was

9.8 days. The difference in LOS compared to RARC in male patients was not significant^[16,19], as was the comparison between female RARC and ORC^[18].

We found that the postoperative complication rate after RARC was barely above 30%, with a high CCS complication rate (≥ 3) of only 12%. A recent review analyzing the evidence and most recent findings on gender-specific differences in BCa considering treatment and outcomes pointed out that women had a significantly longer LOS, longer OT, higher 90-day mortality, and higher postoperative complication rate^[39]. The results of our research, which focused on robotic surgery, showed that, thus far, the available evidence on the rate of postoperative complications after RARC is still sparse and influenced by low sample sizes, but it could be seen that this rate appears to overlap with the open approach and does not seem to be influenced by gender^[18,19]. This evolution could be due to the use of robotic surgery and should be investigated in further prospective and randomized studies comparing genders and surgical approaches.

Data in the literature regarding the association between higher rates of complications/reoperation/readmission after RARC and gender are conflicting. An in-depth critical analysis of complications following RARC and ICUD by Tan *et al.*^[40] found that the male gender was significantly associated with the occurrence of 90-day major complications (OR = 6.98, 95%CI: 1.45-33.58, $P = 0.015$). As the authors pointed out, however, this finding may be skewed by the threefold higher number of male patients. Sharma *et al.*^[26], in their study focusing on the comparison between ORC and RARC in surgical control, found that female sex is not significantly related to an increased risk of 30-day complications in pT3/T4 patients after RC. In the study by Hussein *et al.*^[41], there was no evidence of a statistically significant influence of gender on the risk of reoperation after RARC. Al-Daghmin *et al.*^[42], instead, showed that female gender (OR = 0.41, 95%CI: 0.20-0.83, $P = 0.014$) and BMI ($P = 0.004$) were independent predictors of 90-day readmissions in their multivariable analysis. Only two articles collected by our research dealt with readmission rates among women who underwent RARC. These studies showed that, considering the first 90 days after surgery, almost 30% of patients needed readmission. The difference between the risk of readmission after RC in female patients was not found to be significantly influenced by the surgical approach^[18]. These findings are consistent with the results shown by two relevant population-based analysis comparing RARC and ORC including male and female patients^[24,43], but they differ from what was found in a recent multicenter contemporary retrospective cohort comparative study by Soria *et al.*^[30], in which the readmission rate after RARC was significantly higher than after ORC. The authors attributed this difference to the shortening of the LOS evidenced after RARC.

The main long-term complication that leads to reoperation in female patients who underwent RC is vaginal dehiscence^[44]. The literature regarding this rare but potentially devastating complication is quite scarce; however, it is important to report the relatively high percentage (7%) of patients who underwent laparoscopic RC who required emergency surgical reoperation for transvaginal bowel evisceration due to vaginal dehiscence recorded in the study by Kanno *et al.*^[44]. The authors, also citing the work by Cronin *et al.*^[45], hypothesized an association between higher incidence of vaginal dehiscence and minimally invasive approach, which could be due to overuse of electrocautery during colpotomy or inadequate suturing caused by difficulty in suturing the bottom of the pelvic floor. Considering also the high median age of these patients (82 years old), according to the authors, a vagina-preserving approach might be one option for older female patients during RC, if possible. According to Lin *et al.*^[46], the authors of the largest case series documenting vaginal failure after RARC and ICUD, prophylactically addressing potential vaginal prolapse at the time of extirpative surgery is an emerging issue. However, considering the rarity of vaginal failure in RARC, these procedures need to be carefully deliberated.

We found that the rate of PSMs in women undergoing RARC was only 2.5%, and that of pN+ was 12.72%. Comparing ORC and RARC, no significant difference was found regarding PSMs or pN+^[18]. The study by Matulewicz *et al.*^[27], instead, showed that female sex was significantly correlated with a higher risk of PSMs ($P = 0.001$), but this difference was significant especially in ORC (male *vs.* Female: 11.8 *vs.* 15.2) compared to RARC (11.0 *vs.* 10.2); in addition, in the study by Sharma *et al.*^[26], the increased incidence of PSMs in women did not achieve significance on multivariable analysis. An important pathological outcome on which the literature is not consistent is the LN yield: in some studies, this was significantly increased with RARC^[18,24,27], while, in others, the LN yield was similar between open and robotic techniques^[9,26]. Based on the findings in our review, restricting the cohort to women only, the impact of robotic surgery appears significant in the number of LNs removed, although the topic should be further investigated given the paucity of available data^[18]. Moreover, based on the reviewed studies, gender does not seem to affect LN yield^[16,19].

Previous systematic reviews focusing on functional outcomes in female patients undergoing RC have found a preponderance of small retrospective studies with significant heterogeneity on this topic^[5,12,47-49]. The urinary function was the most well-studied outcome with daytime UI, nighttime UI, and self-catheterization rates ranging significantly across studies due to heterogeneity in definitions for continence, inclusion criteria, and lack of questionnaire adoption^[13,47]. In a systematic review aimed to evaluate female sexual dysfunction post RC, considering it an important predictor of HRQoL, the authors found that the most frequently reported sexual disorders were loss of sexual desire and orgasmic disorders (49% and 39% respectively); however, they highlighted the lack of use of standardized instruments to adequately assess functional outcomes of RC in women^[48].

Research in the field of genital-sparing cystectomy (GSC) techniques to improve functional outcomes after cystectomy is gaining prominence^[50]. Gross *et al.*^[51] and Wishahi *et al.*^[52] recently investigated the impact of GSC and subsequent ONB compared with standard RC in maintaining functional outcomes such as urinary continence in women. The former found superior continence rates for GSC and ONB compared with standard RC, without a negative impact on oncological outcome^[51]. The latter showed that GSC with ONB led to a minimal incidence of hypercontinence (7.80%), while standard RC led to a higher incidence (28.88%)^[52]. A recent systematic review of the literature regarding OSC techniques showed that preservation of the genital or pelvic organs, in both men and women, yields better sexual outcomes than standard RC without compromising oncologic outcomes; however, the authors emphasized that none of these techniques could be recommended as superior to standard RC, and that large-scale prospective and multi-institutional studies are needed to identify patients suitable for these techniques^[50].

According to our research, the results on functional outcomes inherent to RC in female patients are scarce, and those related specifically to the robotic approach are even more reduced: only three studies collected dealt with this issue, and all of them analyzed the topic on a cohort of patients undergoing NS or SS-RARC and subsequent iN. The achieved results vary widely depending on the follow-up time of the patients. While the study by Canda *et al.*^[21] showed poor outcomes related to continence in the two female patients available with a follow-up of only 5-6 months, the results of Tyritzis *et al.*^[22] already show a recovery of both daytime and nighttime continence in female patients at 6 months (40%), which was further improved at 12-month follow-up (66.7%). Even more promising results were achieved in the recent study by Tuderti *et al.*^[13], in which continence reached even higher percentages of female patients (90.9% daytime, 86.4% nighttime). In our results, hypercontinence and subsequent need for CIC ranged from 12.5% to 27.2%. These results are consistent with what has been shown by previous systematic reviews on the subject that collected data on patients of both genders^[5,47,49].

The paucity of available data as well as the heterogeneity in outcome definition, measurement, and reporting has hampered the usefulness of the current evidence base on female sexual function after RARC and UD. However, the results shown appear promising with a percentage of sexually active women at the 12-month evaluation ranging from 66.7% to 72.7%^[13,22]. Using FSFI, after an initial worsening of the results over the first 3 months after surgery, it is possible to denote a significant improvement at 12 months of follow-up, even if in comparison with the baseline the results remain significantly reduced. These results support what was already highlighted by Bhatt *et al.*^[53] in their study on a subset of women who underwent RC with neurovascular preservation and ONB. They found that FSFI score could be preserved compared with women who did not undergo NS, who had a significant decline.

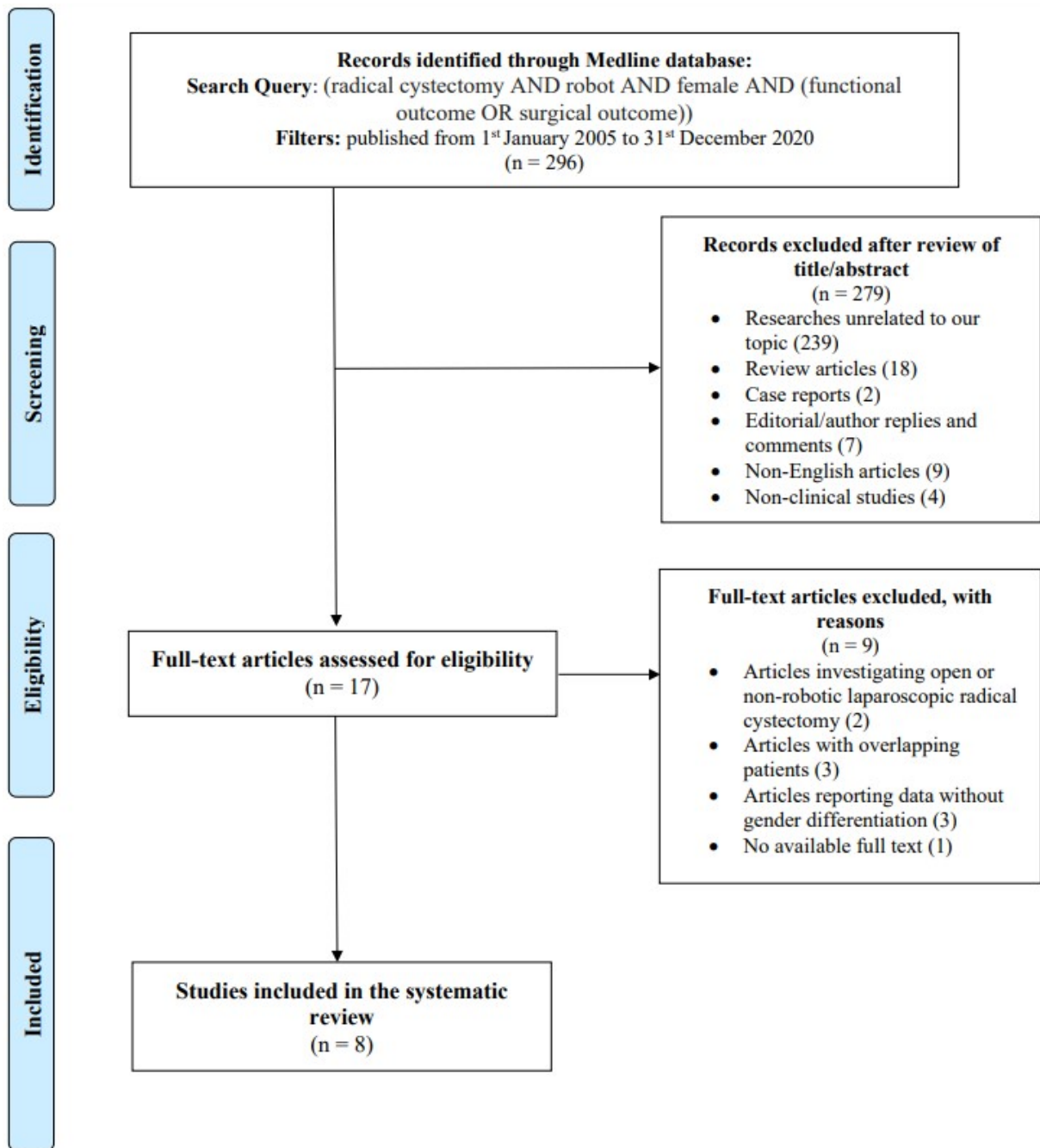
As already known from previous studies, significant differences in emotional problems, role functioning, fatigue, and appetite were noted among women undergoing RC compared with controls of the general population^[47]. One study specifically compared outcomes of men compared with women undergoing RC and ileal conduit and found that men have worse sexual function outcomes than women, whereas women experience a greater burden in postoperative cognitive function and future perspective^[54]. The data available in the literature on the impact of different types of UD on HRQoL show a significant advantage of ileal ONB compared to ileal conduit in terms of HRQoL^[55]. Based on the findings of Tuderti *et al.*^[13], using the EORTC-QLQ-C30 questionnaire among female patients who underwent RARC and iN, global health status/QoL and physical and emotional functioning items improved significantly over time (all $P \leq 0.04$).

It is important to remember that evidence in the literature for functional outcomes after RARC in female patients is relatively recent and, for the moment, we lack objective measurements and standardized methods of detection of important outcomes such as urinary continence, sexual function, and QoL^[12]. The current need is therefore for more in-depth evaluations in randomized controlled trials with prolonged follow-up to identify the most appropriate surgical procedure for the specific patient and improve preoperative counseling.

Our systematic review has some limitations. First, the studies collected were all retrospective and most of them were based on single-center cohorts. Therefore, the results may have been exposed to selection bias or bias due to missing data. Second, the sample size was in many cases extremely low, which may have influenced the results by abnormally increasing their significance. Third, the median follow-up of the collected studies was generally short, which may have affected an accurate description of postoperative long-term complications and a proper characterization of functional recovery; prospective randomized studies with extended follow-up would be useful to determine more accurately post-RARC functional outcomes and long-term surgical outcomes. Fourth, our research was limited to English-language records, which may have affected the choice of eligible items.

Conclusions

RARC and UD for BCa in female patients is a feasible procedure with surgical outcomes overlapping with those in the male patient population. The comparison between RARC and ORC in the female cohort showed a non-inferiority of the robotic approach in terms of postoperative complications and readmission with the added possibility of reducing EBL and increasing the LN yield even if at the expense of a prolonged OT. Postoperative functional outcomes on continence, sexual function, and QoL are still poorly investigated in the available literature, although results inherent in the NS approach appear promising. More standardized templates for reporting functional outcomes as well as randomized prospective studies to better compare techniques and provide the best counseling are required.



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Figure 1. PRISMA flow chart for the article selection process to analyze surgical and functional outcomes in female patients with bladder cancer treated with robot-assisted radical cystectomy (RARC).

DECLARATIONS

Authors' contributions

Contributed sufficiently to the scientific work and share collective responsibility and accountability for the results: Ornaghi PI, Tafuri A, Orlando R, Panunzio A, Moschini M, Afferi L, Lonati C, Cerruto MA, Antonelli A

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Ethical approval and consent to participate

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Consent for publication

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Original Article

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Single position lateral lumbar interbody fusion and pedicle screw fixation: preliminary experience and perioperative results

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Abstract

Aim: The purpose of this study was to review a single surgeon's preliminary experiences with minimally invasive single lateral position anterior-to-psoas lumbar interbody fusion with multiple techniques of percutaneous pedicle screws and present perioperative results and complication rates.

Methods: After obtaining Institutional Review Board approval, thirty-five consecutive patients undergoing, in 2018-2020, single position lateral interbody fusion with posterior fixation after obtaining written informed consent. Pedicle screw accuracy, screw-related complications, overall and segmental lumbar lordosis, intraoperative data, perioperative complications, and Visual Analog Pain Scale (VAS) at 6 months follow-up were collected.

Results: One hundred sixty-nine pedicle screws were placed in 35 patients with a 95.3% accuracy rate. 6/7 breaches measured < 2 mm. No complications or reoperations were performed in relation to screw malposition. Mean preoperative overall lumbar lordosis was $45.6^\circ \pm 12.5^\circ$ (range, 19° - 71°), and $50.3^\circ \pm 9.6^\circ$ (range, 25° - 67°) at 6 months follow up. Mean preoperative VAS scores were 7.3 ± 1.2 (range, 5-10) and 7.3 ± 1.3 (range, 5-10) for the back and leg, respectively and at 6 months follow up, 2.6 ± 2.3 (range, 0-7) and 2.6 ± 2.2 (range, 0-7) for the back and leg, respectively. The mean total operative time was 152.2 ± 54.8 min (range, 80-320 min).



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Conclusion: Single lateral position antepsoas lumbar interbody fusion with bilateral percutaneous pedicle screws and rod fixation report comparable screw accuracy rates, operative times, and lordosis correction with the published literature. This modified technique eliminates the resources and time related to intraoperative prone repositioning and may lead to significant cost savings.

Keywords: Lumbar interbody fusion, extreme lateral interbody fusion, pedicle screw, computer-assisted navigation, minimally invasive surgery

INTRODUCTION

Non-specific back pain due to degenerative lumbar disorders significantly reduces patient function, increases pain scores, and impair quality of life^[1,2]. Lumbar interbody fusion (LIF) surgery has been widely used as a viable option in treating lower back pain and associated neurological disorders refractory to conservative treatment^[3,4]. Several options for open and minimally invasive surgical LIF include posterior or transforaminal lumbar interbody fusion (P/TLIF) or anterior lumbar interbody fusion (ALIF)^[5,6].

Recently, a more minimally invasive, lateral lumbar interbody fusion (LLIF) is attracting attention with two main approaches; the transpsoas, direct LIF, and anterior-to-psoas, oblique LIF^[7,8]. Although these LLIF approaches have not yet gained universal acceptance, early results show similar advantages to ALIF due to its large intervertebral spacer providing restoration of alignment and effective indirect neural decompression. The LLIF approaches also significantly mitigate the many approach-related visceral, vascular, and reproductive complications seen in ALIF^[9-15].

LLIF traditionally requires intraoperative patient repositioning from the lateral decubitus to the prone position to complete supplementary posterior instrumentation with bilateral pedicle screws^[16]. Repositioning requires additional prepping, draping, and room positioning, which may significantly increase costs, operative time, risk of contamination, possible graft migration, and anaesthesia related complications^[17-20]. Furthermore, the lateral position tends to be better tolerated by patients compared to prone surgery and avoids many of the major complications associated with the prone position, such as postoperative vision loss, cardiac arrest/complications, reduced pulmonary compliance, and nerve palsies^[21-23].

Theoretical concerns regarding lateral position bilateral pedicle screw insertion have been raised, namely inadequate correction of lumbar lordosis as well as difficulty with pedicle screw placement^[24-26]. However, several radiographic studies have reported unchanged lumbar lordosis between the prone and lateral positions after LLIF^[27,28].

The literature regarding single position LLIF with posterior fixation is increasing, but it has not been adopted universally yet^[29]. The purpose of this study was to review a single surgeon's preliminary experiences with single lateral position anterior-to-psoas lumbar interbody fusion with different techniques of bilateral percutaneous pedicle screws and present perioperative results and complication rates.

METHODS

A retrospective review of collected data was performed on 35 consecutive patients who underwent single-position antepsoas LIF with bilateral percutaneous pedicle screws and rod fixation at a single institution during October 2018 to February 2020. Informed consent was obtained from all patients prior to the procedure and once again confirmed at their 6-month follow-up appointment. After obtaining institutional

review board (IRB) approval, we reviewed the patients' medical records, spinal radiographs, computer tomography (CT), and magnetic resonance imaging (MRI). Patient demographics, lumbar pathology, comorbidities, and the lists of surgical managements performed, including past, index, and subsequent operations, were recorded. Surgical details such as the operative technique, number of operative levels, total operative time, perioperative complications, reoperation, and length of hospital stay were noted.

Surgical indication was patients who presented with severe back and/or radiculopathy that was refractory to a trial of conservative treatment, including physical therapy, non-steroidal anti-inflammatory medication, narcotics, and steroid injections. Inclusion criteria were patients over the age of 18 undergoing single lateral decubitus position antepsoas lateral lumbar interbody fusion with bilateral percutaneous screws for any degenerative lumbar pathology [Figure 1]. Exclusion criteria included patients with inadequate preoperative imaging available for review and those undergoing combined procedures such as a direct posterior decompression or transforaminal lumbar interbody fusion. All operations were performed by a single surgeon (John Choi), and as such slight selection bias was present.

Surgical technique

Patient positioning

Patient is positioned in the lateral decubitus position with the left side up one-fourth the way from the surgeon on a flat Jackson table. The hip is positioned at the break of the operating table and gently flexed to relax the psoas muscle and femoral nerve. A pillow is placed between the knees, the taping of the lower pelvis and the uppermost hip and femur is performed to stabilise the spine and allow gentle traction of the pelvis. Anteroposterior fluoroscopy is used to ensure that the spine is not rotated, and lateral fluoroscopy is performed to ensure that the disc space is perpendicular to the floor. Care is then taken to further stabilise the patient in the lateral decubitus position with padding of the extremities and the chest, and the skin overlying the disc spaces are marked.

Optimal patient positioning is vital for single position LLIF; positioning too far from the table's edge can limit the surgeon's ability to drop their hand low enough to medialise the downside pedicle, whilst positioning too close to the table can cause interference with the lateral fluoroscopy. Similar to Blizzard *et al.*^[17], a location one-fourth the way across the bed from the surgeon was chosen^[17]. Additionally, slightly rotating the table allowed the surgeon to more appropriately drop their hand and medialise the downside pedicle screw while also bringing the peritoneal sac further away from the spine and psoas and aiding in the anterior dissection.

Antepsoas lumbar interbody fusion

Modified surgical technique for the antepsoas lumbar interbody fusion described by Silvestre *et al.*^[11] was used in our study^[11]. A 4 cm skin incision of the lateral abdomen, centred on the spinal segment and parallel to the external oblique muscle fibres, was made. Abdominal wall muscles were then dissected with a muscle-splitting approach, and the retroperitoneal space was accessed by blunt dissection. The anatomical oblique lateral corridor was exposed by the anterior mobilisation of the peritoneal contents and careful retraction of the psoas muscle.

Radiolucent spine-mounted retractor systems with direct illumination were used to expose and visualise the intervertebral disc. Fluoroscopy was performed to confirm the proper spinal level and a discectomy centred on the anterior half of the disc space was then completed. Disc removal and contralateral annulus release with a Cobb dissector provided the potential for placing a large implant resting on both lateral margins of the epiphyseal ring, and maximising endplate support. Endplates were prepared to expose the subchondral

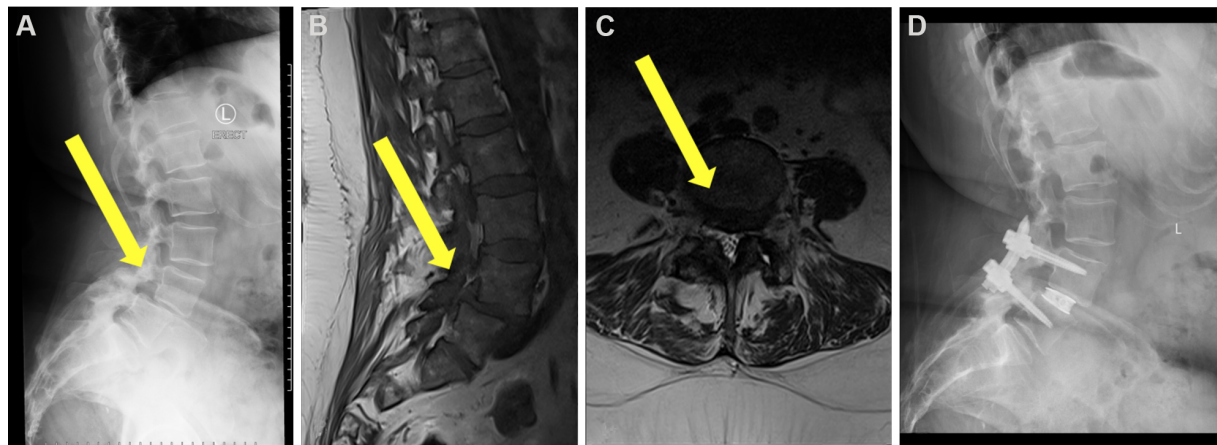


Figure 1. Patient 24. Treatment of degenerative spondylolisthesis of L4/5. (A) Preoperative lateral radiograph, (B) preoperative mid-sagittal magnetic resonance imaging slice, (C) preoperative coronal slice at pathology, (D) postoperative lateral radiograph.

bone, and interbody cage was appropriately sized. Standard lateral cage was inserted across the disc space to gaining bilateral cortical endplate coverage.

Due to the mobility of the abdominal wall, up to three intervertebral discs could be approached using the same 4 cm incision by utilising the “sliding window” technique. However, in some cases with more than two levels, the surgeon split the deeper two muscles twice, having extended the external oblique split to access the disc space.

Bilateral percutaneous pedicle screws

After interbody cage placement, posterior bilateral pedicle screw fixation was performed by either fluoroscopy, CT navigation, or robot-assisted techniques, all of which have been previously described in the literature^[17,30,31]. The method of pedicle screw placement was carefully planned preoperatively and agreed upon by the informed decision of the patient and surgeon’s discretion.

For fluoroscopy-guided pedicle screws, anteroposterior (AP) radiographs were taken to mark the lateral borders of the pedicle, and a lateral view was shown to mark the centre of the pedicles. Percutaneous exposure was made by a small stab incision 2 cm lateral to the lateral border of each pedicle. Pedicle access needle was inserted by tactile feedback at the junction of the superior articular process and transverse process, and then cannulated by using alternating AP and lateral fluoroscopy. K-wires were then inserted and used to confirm the intact walls of the pedicle, and an appropriately sized pedicle screw was placed over the wires. Careful attention was given throughout this process to maintain medial angulation adequately.

For the CT-navigated system, pedicle screw trajectories were firstly planned preoperatively. Intraoperatively, a dynamic reference base and surveillance markers were placed, and an intraoperative CT was performed to obtain the image coordinate system. By utilising the navigation system, the skin over the pedicle screws was marked, and a small stab incises 2 cm lateral to the border of the pedicle was made. The junction between the transverse process and superior articular process was found by blunt dissection, and the pedicle was tapped and drilled under navigation guidance. Pedicle screws were then inserted using CT navigation with the previously planned trajectories.

For patients opting for robot-assisted pedicle screw insertions, a 3rd generation floor mounted robot (ExcelsiusGPS, Globus Medical, Inc. Audubon, PA, USA) was utilised. Similar to the CT navigation system, a dynamic reference base and surveillance markers were placed, and the image coordinate system was obtained from a portable intraoperative CT. From there, pedicle screw trajectory planning was performed. A surgeon-controlled foot pedal was then used to activate and position the robot arm to the planned pedicle trajectory. Small stab incisions were used, and guide holes were created and tapped. Pedicle screws were then inserted by the surgeon under assistance from the robotic arm.

After the insertion of the pedicle screws, a rod was passed percutaneously and secured the pedicle screw head using torque-limiting locking caps. Intraoperative fluoroscopy was then utilised to verify the pedicle screw, interbody spacer, and rod position.

Outcomes

CT scans were routinely obtained 6 months postoperatively to assess fusion and hardware placement and integrity. Screw accuracy was evaluated using the technique seen by Spitz *et al.*^[32], where screw breaches were graded based upon the magnitude and direction of the breach; A = 0-2 mm, B = 2-4 mm, C \geq 4 mm^[32]. Lumbar lordosis (L1-S1) was obtained by preoperative and 6 months follow-up anteroposterior and lateral radiographs^[33]. All radiographic outcome measures were reviewed by an independent orthopaedic fellow (Mehul Sakar).

Visual Analog Pain Scale (VAS) for the legs and/or back was recorded preoperatively and at 6 months follow-up.

Statistics

Data were presented as mean \pm SD (range). Statistical analysis included descriptive statistics, and two-tailed paired *t*-test or Mann-Whitney *U* test (if non-normally distributed) was used. A *P* value of < 0.05 was defined as statistically significant. Data distributions were evaluated using the Shapiro-Wilks test.

RESULTS

Patient characteristics and results are presented in Table 1. Thirty-five patients (17 males and 18 females) with a mean age at surgery of 69 years (46-87 years) were included in this study. All patients were followed up for a minimum of 6 months after surgery. The mean body mass index (BMI) was 31.9 (22.0-50.9), and 26% of the cohort had a history of smoking whilst 17% had diabetes. Most of the patients had no previous lumbar spine surgery (83%), and those that did had either a laminectomy (9%), microdiscectomy (5%), or PLIF (3%).

Surgical data are presented in [Table 2]. The primary indication for surgery in our cohort included spondylolisthesis (46%), degenerative disc disease (44%), stenosis (5%), and scoliosis (5%). A total of 51 lumbar intervertebral disc levels were operated on, with 23 patients undergoing single-level surgery, 8 undergoing two-level fusions, and 4 undergoing three-level fusions. The most common spinal level treated was L4/5 (22 patients), followed by L5/S1 (21 patients), L3/4 (15 patients), and L2/3 (2 patients). The mean total operative time was 152.2 ± 54.8 min (80-320 min), and the mean length of hospitalization was 5.3 ± 1.7 days (3-9 days).

A total of 169 pedicle screws were placed; 72 screws using fluoroscopy, 10 screws with CT navigation, and 87 with robot assistance. Different techniques were used for pedicle screws placement in part due to the surgeon transitioning from navigation use to robot-assisted technique. Also, fluoroscopic guided

Age (years) /Sex	BMI	Pathology	Operative levels*	BPS technique	OR time (min)	LOS (days)	Screw accuracy				Overall LL		Segmental LL		Pre VAS (back/leg)	Postop VAS (back/leg)	Comment			
							NB	A	B	U	D	Pre	F/U	Pre	F/U					
1	64/F	40.2	SL	L4/5	Fluoro	135	5	4					44	50	19	22	6/6	b		
2	71/F	38.3	SL, DDD	L3-S1	Fluoro	272	9	8					39	54	31	40	7/9			
3	60/F	37.5	DDD	L4/5	Fluoro	100	8	4					29	44	16	20	8/8			
4	84/M	26.7	DDD	L3-L5	Fluoro	172	6	6					50	47	32	32	6/6		L5 fracture, recurrent symptoms, reoperation	
5	65/F	28.5	SL	L4/5	Fluoro	152	3	4					52	55	20	20	8/8			
6	85/M	25.8	SL, ST	L4/5	Fluoro	120	5	4					46	57	21	23	5/5			
7	76/M	35.2	SL	L5/S1	Nav	164	5	4					55	59	20	24	8/8		Partial cage protrusion	
8	73/F	25.0	SL, DDD, ST	L3-L5	Fluoro	129	5	6					52	55	31	33	6/6		Transient neuralgia	
9	76/M	29.4	SL	L4/5	Fluoro	134	7	4					43	40	-8	5	-/5		Delirium, pneumonia	
10	87/F	33.7	DDD	L4-S1	Nav	115	6	6					40	47	13	17	7/7		Persistent symptoms, R/O of cage	
11	77/M	22.0	SL, DDD	L5/S1	Fluoro	130	6	4					40	57	11	25	6/6	b	Transient neuralgia	
12	61/M	30.0	DDD, SC	L4/5	Fluoro	154	3	4					45	50	16	18	8/8		Transient neuralgia	
13	72/F	25.1	SL	L4/5	R	158	6	4					56	56	20	20	-/8		Persistent symptoms, microdiscectomy (L4/5), new onset AF	
14	79/F	33.1	SL, DDD, SC	L5/S1	R	172	3	4					56	56	25	29	8/8		Transient neuralgia	
15	62/M	33.3	DDD	L3-S1	R	320	5	8					30	46	30	38	6/6			
16	60/M	38.0	SC	L2/3	Fluoro	135	3	4					28	40	6	6	8/8			
17	66/M	30.1	SL	L4/5	R	95	4	4					59	59	25	36	8/8			
18	72/M	29.9	DDD	L3/4	R	101	4	4					50	50	9	11	6/6			
19	79/M	31.8	DDD	L3-L5	R	195	6	6					22	25	14	14	7/7			
20	69/F	40.0	DDD	L4-S1	R	297	6	4	1			1	35	45	25	36	8/8		Transient neuralgia - left leg	
21	70/M	22.2	ST	L3/4	Fluoro	80	4	4					46	46	12	14	8/8			
22	72/M	28.7	DDD	L5/S1	Fluoro	175	3	4					47	60	13	34	6/6			
23	76/F	30.2	DDD	L2/3	R	135	9	4					22	25	1	2	10/10		New onset of back pain, microdiscectomy (L4/5, L5/S1)	
24	61/F	34.9	SL	L4/5	R	130	6	4					60	67	24	32	6/6			

25	77/M	34.9	DDD	L3/4	Fluoro	95	6	4			63	63	12	20	10/10	1/1	Transient neuralgia	
26	66/F	36.2	DDD, ST	L3-S1	R	170	9	5	3	1	2	42	44	40	41	8/8	7/7	Postoperative fall, recurrent symptoms, plan for reoperation
27	72/M	29.7	DDD	L3-S1	R	230	5	6	1	1	2	59	55	50	48	6/6	2/2	Persistent left leg/back pain, SIJ fusion
28	75/M	27.7	DDD	L3/4	Fluoro	105	7	4			53	59	12	16	8/8	1/0	Urosepsis, delirium	
29	60/F	27.5	DDD	L3-L5	Fluoro, R	177	4	5	1		1	19	33	0.75	12	5/5	0/1	
30	46/F	38.7	SL	L3/4	Fluoro	118	5	4			54	54	10	10	8/-	2/-	Wound infection	
31	63/F	25.9	SC	L3-L5	Fluoro, R	130	4	6			57	57	19	28	8/8	0/4 ^b		
32	59/M	29.4	ST	L3/4	R	145	4	4			38	46	7	9	8/8			
33	62/F	28.7	SL	L5/S1	R	110	4	4			71	57	35	22	8/8	0/0		
34	61/F	50.9	SL	L4/5	R	147	7	4			51	24	51	26	9/9	7/7	Respiratory distress, prolonged ICU stay	
35	74/F	28.7	SL, ST	L4/5	R	130	6	4			49	56	10	16	7/7	5/5		

*Interbody cage and bilateral pedicle screws. ^bVAS unable to be found. M: Male; F: female; BMI: body mass index; SL: spondylolisthesis; DDD: degenerative disc disease; ST: stenosis; SC: scoliosis; L: lumbar vertebral body; S: sacrum; BPS: bilateral pedicle screw; Fluoro: fluoroscopy; Nav: CT navigation; R: robot assisted; OR: operating room; LOS: length of stay; NB: no breach; A: Spitz grade A breach (< 2 mm); B: Spitz grade B breach (2-4 mm); U: upside screw; D: downside screw; M: medial breach; L: lateral breach; Pre: preoperative; F/U: follow-up; Postop: postoperative.

percutaneous pedicle screw placement was used in two patients due to robot malfunction and in the other cases due to the surgeon's preference. It is important to note that all the techniques can be readily used depending on the availability of the equipment. Six months follow-up CT scans were obtained from 35 (100%) patients. 95.3% of screws were successfully placed with no breaches, and 7 total screw breaches were identified (4.7%); 6 were graded A breaches (< 2 mm), 1 grade B (2-4 mm) [Figure 2], and 0 grade C (> 4 mm) breaches; it showed no statistically significant difference with $P = 0.14$. Of the 7 breached screws, 6 were downside/right-hand side screws, all with lateral breaches, and a medial breach was observed for the 1 upside/left-hand side screw [Table 3]. Based on the surgeon's discretion, 2/87 robot-assisted screws were manually repositioned, both of which were later identified as breaches. In our series, all breach screws were placed with robot assistance, and a clear trend of lateral breach laterality is seen in the downside screws. In our cohort, no complications were reported due to screw placement, and revision surgery was not performed due to screw malposition.

Overall lumbar lordosis improved significantly from $45.6^\circ \pm 12.5^\circ$ (19° - 71°) preoperatively to $50.3^\circ \pm 9.6^\circ$ (25° - 67°) at 6 months follow up ($P < 0.001$). Similarly, segmental lumbar lordosis significantly increased for one-level and two-level lumbar fusions, from $14^\circ \pm 9^\circ$ (-8° - 35°) to $19^\circ \pm 9^\circ$ (2° - 36°) ($P < 0.004$) and $19^\circ \pm 11^\circ$ (0.5° - 32°) to $25^\circ \pm 10^\circ$ (12° - 36°) ($P = 0.03$), respectively at 6 months follow up. For three-level fusions, segmental lordosis did not significantly change ($P = 0.23$) [Table 4].

Table 2. Surgical data

Parameter	Overall
Primary pathology n (%)	
Spondylolisthesis	16 (46%)
Degenerative disc disease	15 (44%)
Scoliosis	2 (5%)
Stenosis	2 (5%)
Number of levels treated n (%)	
1	23 (67%)
2	8 (22%)
3	4 (11%)
Operative time (min), mean \pm SD (range)	152.2 \pm 54.8 (80-320)
Hospital stay (days), mean \pm SD (range)	5.3 \pm 1.7 (3-9)
Future operations	
Microdiscectomy	2
Cage removal	1
Sacroiliac joint fusion	1

Table 3. Screw accuracy

Breach grade	No. of screws	Upside pedicle		Downside pedicle	
		Medial	Lateral	Medial	Lateral
No breach	162 (95.3%)				
Grade A	6 (4.7%)	1			5
Grade B	1 (0%)				1
Grade C	0 (0%)				

$P = 0.14$, represent the comparison between upside and downside pedicle screws.

Table 4. Lumbar lordosis

	Overall LL	One level segmental LL	Two level segmental LL	Three level segmental LL
Preoperative	45.6° \pm 12.5°	14° \pm 9°	19° \pm 11°	38° \pm 9°
Postoperative	50.3° \pm 9.6°	19° \pm 9°	25° \pm 10°	42° \pm 4°
P value*	< 0.001	< 0.004	< 0.03	= 0.23

*Two tailed paired t -test. LL: Lumbar lordosis.

Mean VAS scores for back and leg significantly improved after the index operation, from 7.3 ± 1.2 (5-10) to 2.6 ± 2.3 (0-7) ($P < 0.001$) and 7.3 ± 1.3 (5-10) to 2.6 ± 2.2 (0-7) ($P < 0.001$), respectively at 6 months follow up. Unfortunately, 3 postoperative patients reported VAS scores were unable to be found.

Postoperative pain unrelated to pedicle screw placement included persistent symptoms in 3 patients. Patient 10 experienced complete resolution of back pain but continued to suffer significant leg symptoms postoperatively due to an unexpanded hyperlordotic cage. This cage was subsequently removed. Patient 13 experienced no improvement in back or leg pain and underwent a microdiscectomy and posterior decompression during the follow-up period. Patient 27 reported left leg and back pain 3 months postoperatively, and a sacroiliac joint fusion was conducted. Patients' complications are summarized in Table 1.

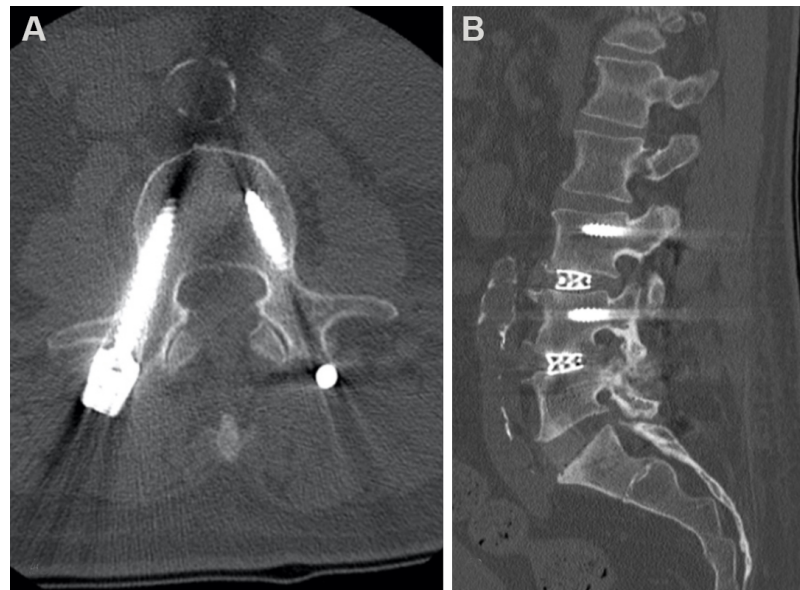


Figure 2. Patient 27. Grade B (2-4 mm) of right hand downside L3 pedicle screw. (A) Postoperative coronal computerized tomography slice, (B) postoperative sagittal computerized tomography slice.

Other complications included delays of the transfer due to bed shortages at rehabilitation centres (6), pneumonia (1), respiratory distress (1), prolonged intensive care unit stay (1), delirium (2), new-onset atrial fibrillation (1), wound infection (1), urinary tract infection (1) and urosepsis (1).

DISCUSSION

Providing high-quality, value-based treatments is essential for the patient's benefit and sustainability of healthcare systems. Alternative forms of surgical techniques with low operative times and procedural morbidities decrease hospital costs, shorten recovery times and improve patient experiences^[34-36]. Traditionally, the prone position is utilized by spine surgeons to gain access to the spinal column^[21-23]. Recently, there has been increasing interest in completing LLIF in the single lateral position, and reports of reduced operative times and consequent cost reductions have been made^[17,18,37]. This study builds on the previous work of Blizzard *et al.*^[17] and Ziino *et al.*^[18], and found favourable outcomes for primary endpoints including, screw accuracy, complication rates, surgical efficiency, and lordosis correction.

Pedicle screw misplacement rates for conventional prone position techniques vary greatly in the literature, ranging from 5% to 41%^[38-42]. It represents the significant heterogeneity in the radiographic modalities and grading schemes used in studies to assess screw accuracy. Breach rates of 1.5% to 14.3% were found when the literature was limited to studies investigating screw accuracy rates with postoperative CT imaging^[17]. Currently, some papers have assessed pedicle screw accuracy in single position LLIF, and Blizzard *et al.*^[17] reported an overall breach rate of 5.1%, with 1.2% of screws between 2-4 mm, whilst Sellin *et al.*^[30], reported a 14% (2/14) overall breach rate in their 4 patient case series. Although there is no comparison cohort in the current study, the 4.7% overall breach rate and 0.7% grade B (2-4 mm) breach rate is consistent with the published literature. Moreover, the surgeon used the different techniques available, including robots, navigation, and fluoroscopic guided percutaneous pedicle screws. It can be helpful as robots and navigation are unable to use in every operating theatre in the world.

Theoretical concerns regarding the medialization of downside pedicle screws during single position LLIF with posterior fixation have been raised. In this study, 6/7 breaches were identified on the downside screw with lateral laterality, which contrasts the lack of clear trends seen by Blizzard *et al.*^[17]. Comparatively, Hiyama *et al.*^[43] found that all breaches occurred on the lateral side. These results may validate the concerns of the surgeon's potential inability to drop their hands low enough for lateral position screw insertion. However, it must be noted that all breaches in this study occurred with the robot-assisted technique, and no breaches were found for the navigation or fluoroscopy-guided pedicle screw. It indicates that accurate downside screw placements with adequate medialisation can be established in the lateral position. This discrepancy between techniques can possibly be explained by the live intraoperative assessment and corrections that are made during fluoroscopic screw insertion. It could also be due to the movement of the dynamic reference base of the robot. Furthermore, the surgeon's familiarity with the prone fluoroscopic percutaneous pedicle screw technique may allow them to readily adapt the technique for the lateral position, similar to Blizzard *et al.*^[17], we did not appreciate a significant learning curve for the technique.

Huntsman *et al.*^[31] reported on the feasibility of single position robot-assisted pedicle insertion, although all the breaches of our study were associated with the robot, only 8% of robot-assisted screws were breach, with 1% of the breaches being greater than 2 mm. These results remain comparable with the literature as breach rates of 3 mm or greater, ranged from 3.7% to 9.7% for fluoroscopic prone position pedicle screw insertions^[17]. Similar to the fluoroscopic technique, there was no apparent learning curve associated with the robot-assisted technique, and pedicle screw placement is controlled and performed by the surgeon's discretion and guidance. Regardless of the technique utilized for single lateral position pedicle screw insertion after LLIF, our pedicle screw accuracy rates are consistent with the published literature.

Due to inconsistent criterion amongst surgeons, screw-related complication and reoperation rates are difficult to interpret amongst the published literature. Misplaced pedicle screws may result in significant injury to the nerve roots, spinal cord, vasculature, viscera, or cardiopulmonary system, all of which are potential threats to limb and life^[42-45]. However, despite neural structures lying within 2 mm of the pedicle, complications are shown to be associated with breaches of 4 mm or more^[46]. In the current study, we adopted a low threshold for reoperation, monitoring for new or persistent perioperative radiculopathies correlated with the pedicle screw vertebral level. No screws breaches greater than 4 mm were identified, and in line with the literature, 0 screw malposition-related complications were found, and consequently, no revision surgeries were performed^[17,31,47].

The current study exclusively investigating single-lateral-position multilevel antepsoas LLIF with posterior fixation, and a mean operative time of 152 min was found. These results align with other multilevel single position studies. Ziino *et al.*^[18] reported an operative time of 149.2 min whilst Huntsman *et al.*^[31] noted an operative time of 155.7 min. Additionally, in Ziino *et al.*^[18]'s comparative study, the operative time of the dual position procedure was 44 min longer than the single position counterpart. A time saving of 44 min is substantial, and the majority of this time is likely from patient wound closure, re-positioning, re-prepping, and re-draping. A recent multicentre cohort review found that longer operative times are associated with a step-wise increase in overall, medical, and surgical complications rates^[48]. Furthermore, the reduced operative time for single position LLIF may significantly reduce operative costs, with some papers suggesting a potential \$ 3154 saving per case^[17,49]. Therefore, we suggest that spine surgeons who frequently perform lateral surgery consider the implementation of single position surgery.

Sagittal alignment is well-documented as the most critical and reliable radiographic predictor for patients' quality of life, and imbalances exacerbate patient-reported pain, function, and self-image^[50,51]. Supporters of

dual position surgery often argue that optimum restoration of lordosis is only obtained with the prone position^[25,52,53]. However, recently radiographic studies reported no additional lordosis correction from lateral-to-prone repositioning after the insertion of an interbody cage^[27,28]. In the present study, overall, one-level and two-level lumbar lordosis significantly improved by a mean of 4.7°, 5°, and 6°, respectively. These results are consistent with recent systematic reviews investigating lordosis correction of LLIF with prone repositioning^[54-56]. Furthermore, comparative studies have shown no significant difference in lordosis correction between the single lateral position LIF and lateral-to-prone repositioned techniques^[18,57]. It suggests that adequate lordosis restoration can be achieved in the single lateral decubitus position, with no additional advantage from repositioning.

This study has several limitations. First, although this study has known limitations and biases relating to a retrospective, single-cohort study design, the results were consistent with the findings in the literature. Second, multiple pedicle screw insertion techniques were included in this study. However, the purpose of this study was to describe a surgeon's preliminary experience with single position LLIF with bilateral pedicle screw fixation and report on the short-term outcomes and complications of this modified technique. Future studies should compare the three current pedicle screw techniques of fluoroscopy, CT navigation, and robot assistance, especially investigating operative times, radiation times, and doses. Third, the surgeon performed his first cases with this particular robot which has its learning curve.

In conclusion, we presented in this study a surgeon's preliminary experience with a single position, multilevel antepsoas LIF with bilateral percutaneous pedicle screws and rod fixation and report comparable screw accuracy, overall complication rates, operative times, and lordosis correction with the published literature. This modified technique eliminates the resources and time related to intraoperative prone repositioning and may lead to significant cost savings. It can be done with fluoroscopy guidance, navigation, or robot.

DECLARATIONS

Authors' contributions

Supervisor of the research project, patient recruitment, writing and editing of the manuscript, main surgeon: Choi J

Writing and editing of the manuscript, data collection, data analysis: Rhee I

Writing and editing of the manuscript, data analysis: Sakar M

Writing of the manuscript, data collection: Park I

Writing and editing of the manuscript, data collection, data analysis, corresponding author: Maalouly J

Availability of data and materials

Available upon request.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Written informed consent, and IRB approval obtained.

Consent for publication

Written informed consent.

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Review

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The contemporary status of robotic intracorporeal neobladder

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Abstract

Robotic intracorporeal neobladder (RIN) is increasingly the modality of choice for intracorporeal urinary diversion in high-volume Robotic Urology centers. This article details the modern technique of RIN, explains specific tips and tricks to facilitate timely operative progression as well as weighs the outcomes from recently published series. An OVID/EMBASE database search was done using keywords: robotic, cystectomy, intracorporeal neobladder, orthotopic, and intracorporeal urinary diversion. The inclusion criteria were original studies on Robot-Assisted Radical Cystectomy (RARC) with RIN series, available in full text in English, published over the last ten years with a specific analysis of oncological and functional outcomes. Pooled data analysis of the 10 studies included shows 80% of patients had organ-confined disease ($\leq pT2$), 1.86% of patients had positive surgical margin, median lymph node yield of 23 nodes (IQR = 7.5), and cancer-specific survival rate of 78% (range 72%-100%) over a mean follow up of 27.43 months (range 13-37 months). Functionally, the median day continence rate is 81.5%, night continence rate is 61%, and rate of return to spontaneous sexual activity is 33.5%. This compares favorably with outcomes of The International Robotic Cystectomy Consortium - Extracorporeal Urinary Diversion data and data from open radical cystectomy (ORC) neobladder series with long term follow up. High-volume robotic centers have successfully introduced programs for RARC, with RIN demonstrating its safety and feasibility. Their results suggest potential to improve perioperative and functional outcomes over ORC. Moreover, under mentorship, surgeons can learn the technique of RARC and RIN without these outcomes being significantly affected.



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Keywords: Neobladder, cystectomy, robotic, intracorporeal, orthotopic

INTRODUCTION

Surgical treatment of muscle-invasive (MIBC) and high-risk non-muscle-invasive bladder cancer is uniformly recommended. However, despite the emergence and global spread of robotic techniques, there is still some controversy over the suggested advantage of robotic-assisted over open approaches. Moreover, the choice of intracorporeal urinary diversion (ICUD), which is technically challenging, adds to this debate, further polarised by robotic intracorporeal neobladder (RIN), the most difficult technical option of all. Nevertheless, robotic cystectomies remain steadfast in their belief that their approach is superior despite the lack of clear scientific proof by randomized controlled trials. It is reflected in the widespread adoption of RARC and RIN by high-volume robotic urological centers. Between 2015 and 2018, 70% in North America and 50% in Europe of Radical Cystectomy (RCs) performed were done robotically^[1], with an increase in ICUD from 9% to 97% between 2005 and 2015^[2]. This increase in ICUD was primarily accounted for by centers performing intracorporeal ileal conduit, which increased from 2% to 81%, rather than RIN, which only increased from 7% to 17%^[2]. RIN is regarded as one of the most technically challenging procedures in robotic urology. Its steep learning curve (LC), lack of indisputable evidence of patient benefit, and the economic drawbacks of prolonged theater time may all explain why its widespread adoption has been slower. Nevertheless, as urological centers gain experience with clearly defined mentorship programs and published outcomes with increasingly long follow-up in appropriately selected patients, RIN has shown to provide equivalent oncological outcomes and long-term quality of life (QoL) compared to the open approach. This review will detail the current techniques for RIN, highlight patient selection, discuss the results of published series to date as well as key ongoing trials and outline some of the related issues, including Enhanced Recovery after Surgery (ERAS) protocols, the LC for the procedure and economics.

Patient selection

Patient selection is crucial to a successful operative outcome and will be influenced by surgeon experience, clinical factors affecting the decision to undertake a robotic procedure, and specific patient factors related to the choice of neobladder itself. Generally, the ideal patient for Robot-Assisted Radical Cystectomy (RARC) will be under 75 years of age, slim with a BMI of less than 30, have a T2 tumor without locally advanced disease, have good performance status with minimal co-morbidities, and no history of prior abdominal radiation or surgery^[3]. As surgeons gain experience, these guidelines will be flexed, but whatever the surgeon experience is, patients with BMI > 35, complex cardio-respiratory co-morbidities and prior abdominal or vascular surgery, pelvic trauma or radiotherapy, and locally advanced disease will prove challenging. Even with these factors in mind, further consideration is required when selecting patients for RIN, such as the physiological and cognitive requirements to adapt to a neobladder that can significantly impact the outcome and patient's quality of life. The main contraindications for orthotopic neobladder are renal and liver impairment, tumor invading the prostatic apex and bladder neck (which would result in a positive intraoperative urethral margin). In addition, there are relative contraindications as the lack of patient's motivation or cognitive impairment, preventing adherence to the bladder-training program, physical limitations hinder the ability to intermittently self-catheterize, and a damaged urethral sphincter that would result in severe incontinence^[4].

Technique

To date in the literature, the majority of published series have used the Studer U modified neobladder, the largest series of which was from Karolinska detailing the technique and outcomes of 158 patients since its introduction in 2003^[5]. Other techniques used for RIN include modified Hautmann W, the Padua, the Y technique, the Florence, the Vescica Ileale Padovana, the Pyramid pouch, and the Camey Reservoir^[6]. This

review will focus on the Karolinska modified Studer U technique, which is the procedure that the authors have the most experience in and was also the most common technique used in our series review [Table 1].

Patient preparation, set up, and trocar positioning

Most high-volume robotic centers will engage in ERAS protocols for robotic cystectomy and ICUD^[7]. Regarding preoperative patient advice, ERAS protocols now recommend written and oral counselling and education on the nature of the procedure and postoperative care as well as preoperative medical optimization. Mechanical bowel preparation can be avoided; suitable patients should be encouraged to have preoperative carbohydrate loading. In the 24 h prior to surgery, they should adopt a low residue diet, with solids and clear fluids for 6 and 2 h respectively^[7].

In the operating room (OR), the patient is placed under general anesthesia and in the lithotomy position with the operating table at maximum Trendelenburg position. Pneumatic calf compression is applied to reduce the risk of deep vein thrombosis, the patient's arms are fixed along their sides, and a body warmer is used over the thorax to prevent hypothermia. Antibiotic prophylaxis with broad-spectrum antibiotics should be given at induction, and low molecular weight heparin is given in the early postoperative period and continued for 4 weeks post-surgery.

Trocar positioning is a crucial part of the procedure; the operation can proceed smoothly by setting up the robotic arms and instrument positions. With the Da Vinci Xi system, the 8 mm camera port is placed first, 1-2 cm to the left of the midline and 3-5 cm above the umbilicus. Next, two further robotic 8 mm ports are placed 8-10 cm right and left of the midline at the level of the umbilicus. The left-sided assistant port is 2-3 cm above and medial to the anterior superior iliac spine (ASIS), as well as 8-10 cm away from the left-sided robotic port. It is a 15 mm port that allows the bowel stapler to pass through during the bowel work and anastomosis. At other times, a robotic 8 mm port with the instrument can be telescoped through it as the "fourth arm". The final two ports are 12 mm assistant ports, the first symmetrically between the camera and right robotic port, and far right, 8-10 cm from the right robotic port, approximately 2-3 cm superior and medial to the right ASIS^[8]. Next, we discuss the neobladder formation and skipping cystectomy part.

THE STUDER U MODIFIED NEOBLADDER (SEE FIGURES 1-18 AND THE "TIPS AND TRICKS" SECTION)

The original description of the Studer U orthotopic neobladder has been modified according to Wiklund and Poulakis^[8] for robotic intracorporeal reconstruction. Although other robotic centers may have their own modifications to Studer's original technique, the fundamental steps are the same^[9]. After trocar placement, the RARC and extended pelvic lymph node dissection (EPLND) are carried out before the RIN. For the purposes of standardization and education, the RIN procedure is then broken down into the following modules:

Demarcation of the neobladder bowel segment [Figure 1]: 50 cm of ileum is identified, at least 25 cm away from the ileo-cecal junction, and brought down into the pelvis in a U shape. The "tip" of the U is the site of the urethro-ileal anastomosis (UIA). The right ileal limb above the UIA will be 10 cm in length, and the left ileal limb will be 40 cm in length. Bringing the ileum down to the urethra is generally easier in females.

Urethro-ileal anastomosis [Figures 2 and 3]: in keeping with the Rocco principle and to allow a tension-free anastomosis, the posterior aspect of ileal serosa is sutured to the sub-urethral tissues. Following this, a 2 cm incision is made through the ileum into the lumen, and the formal anastomosis is completed using double-needle 3-0 monofilament synthetic absorbable suture (Biosyn). The first sutures are placed on the urethra in

Table 1. Robotic intracorporeal neobladder study series: the perioperative outcomes

Study	Technique of RIN	Number of patients had RARC	Number of patients had RIN	Median OT (min) in RIN	EBL (mL) in RIN	Patients had transfusion in RIN	Number of events of complication Clavien-Dindo \geq III at 30 days in RIN	Number of events of complication Clavien-Dindo \geq III at 90 days in RIN	Median length of hospital stay (days) in RIN
Collins et al. ^[39] 2014	Studer U	147	80	420	n/a	n/a	n/a	n/a	n/a
Goh et al. ^[40] 2012	Studer U	15	8	450	225	3	2	2	8
Hosseini et al. ^[5] 2020	Studer U	158	158	363	300	n/a	35	10	8
Obrecht et al. ^[20] 2020	Modified Studer	12	12	575	600	n/a	n/a	n/a	n/a
Tyritzis et al. ^[41] 2013	Studer U	70	70	420	500	3	22	13	9
Desai et al. ^[42] 2014	Studer U	132	132	456	430	6	20	17	10.6
Tuderti et al. ^[13] 2020	Padua	11	11	255	n/a	n/a	0	n/a	7
Schwentner et al. ^[43] 2015	Studer U	62	62	476	385	n/a	16	16	17
Gu et al. ^[44] 2020	Studer U	12	12	419	400	8	1	1	14.5
Jonsson et al. ^[23] 2011	Modified Studer	45	36	480	625	n/a	3	5	9

RIN: Robotic intracorporeal neobladder; RARC: robot-assisted radical cystectomy; OT: operating time; EBL: estimated blood loss.

to out either side of 6 o'clock, and the suturing is completed circumferentially over a 22 Fr catheter, out to in on the ileal side, and in to out on the urethral side.

Isolation of neobladder bowel segment and re-anastomosis of the bowel [Figure 4]: once the UIA is complete, as described above, the bowel is divided with Endo-GIA™ Laparoscopic staplers which are passed through the “fourth arm” 15 mm port, once the robotic instrument has been removed. It is done 10 cm above the UIA for the right ileal neobladder limb and 40 cm above the UIA for the left ileal neobladder limb. The ileum is then re-anastomosed using both a 60 mm and a 45 mm cartridge, finally closing the upper aspect of the anastomosed bowel with another 60 mm cartridge.

Detubularization of the ileal neobladder limbs and formation of the posterior plate [Figures 5 and 6]: both limbs of the neobladder are opened over the suction instrument, except for 10 cm of the proximal aspect of the left ileal limb, which forms the “chimney”. Once detubularized, stay sutures are placed to bring the medial sides of the top of the right ileal neobladder limb to the medial aspect of the left ileal neobladder limb, just at the bottom of the chimney. Two more stay sutures are placed. First, 10 cm below the chimney, the medial aspect of the left ileal neobladder limb is sutured to the upper aspect of the ileum just above the UIA. It leaves an open U-shaped loop of 20 cm of the left ileal neobladder limb on the left side of the pelvis. The final stay suture is placed at its most lateral aspect, bringing the inner aspect of the upper and lower parts of this loop together. With the stay sutures in place, the different parts of the posterior plate are

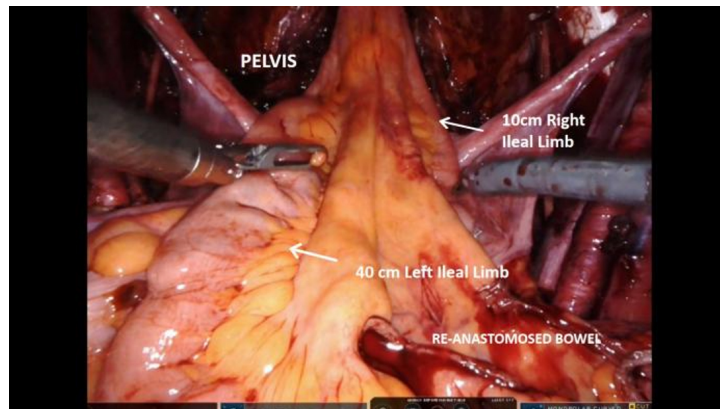


Figure 1. Demarcation of Neobladder bowel segment.

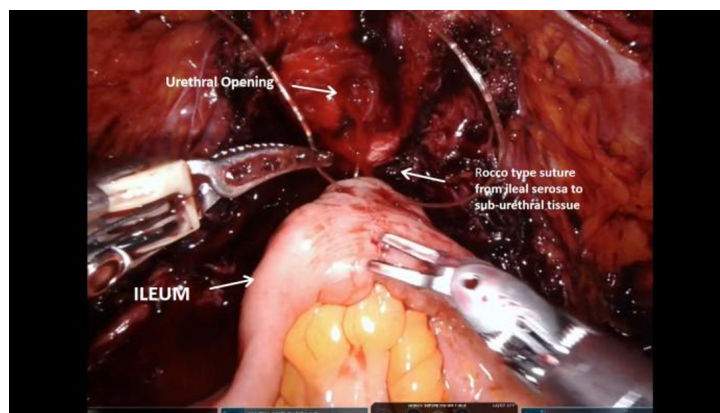


Figure 2. Urethro-ileal anastomosis A.

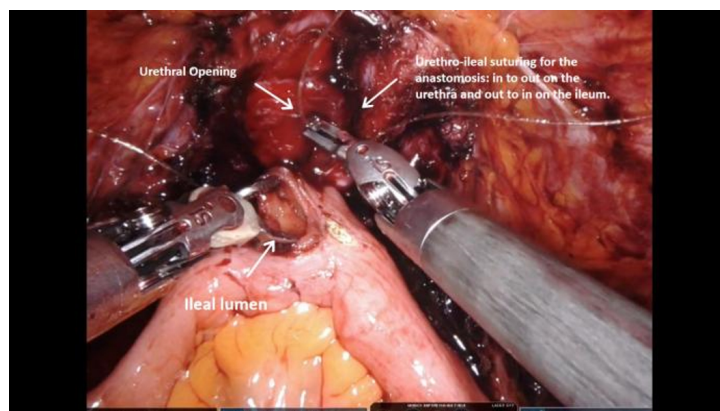


Figure 3. Urethro-ileal anastomosis B.

clearly defined and closed with a 3/0 V-loc™ suture.

Anterior neobladder closure [Figures 7-9]: once the posterior plate has been constructed, the anterior part of the neobladder is closed with a similar 3/0 V-Loc suture; starting by folding the left side of the neobladder

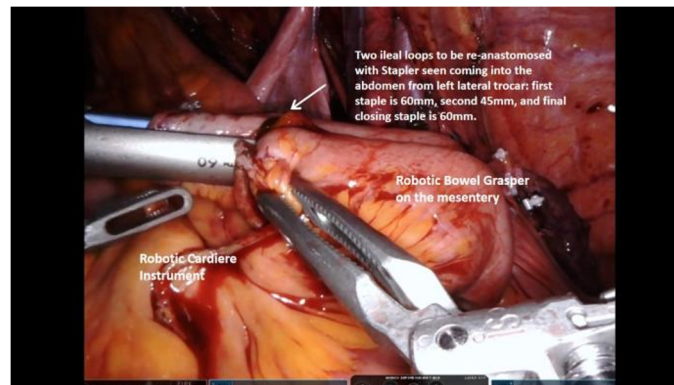


Figure 4. Isolation of neobladder bowel segment and re-anastomosis of the bowel.

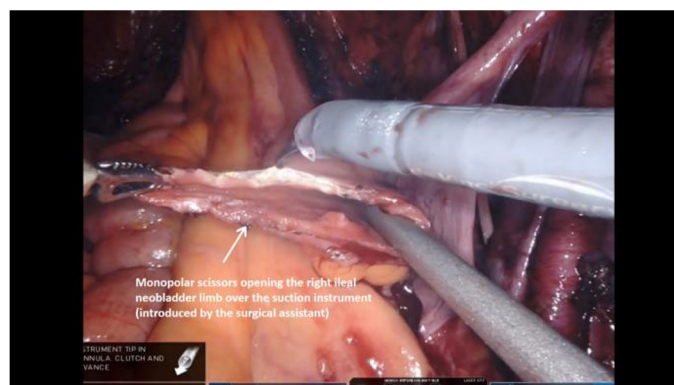


Figure 5. Detubularisation of the ileal neobladder limbs and formation of the posterior plate A.

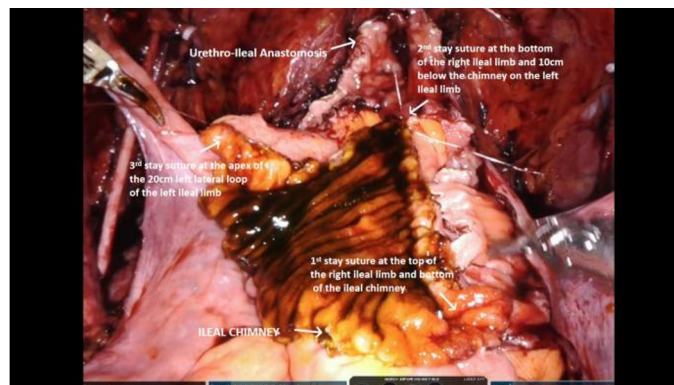


Figure 6. Detubularisation of the ileal neobladder limbs and formation of the posterior plate B.

at the lateral aspect of the left ileal limb lateral loop up to the base of the chimney (see [Figures 7-9](#)), and then continuing distally with a running V-loc suture down to the UIA. At its most proximal aspect, the neobladder is initially left open, in order to pass the ureteric stents.

Uretero-ileal anastomosis, stent insertion, and completion of neobladder closure ([Figures 10-18](#)): a Wallace-type uretero-ileal anastomosis is the used technique. Following the dissection of the ureters at the beginning of the cystectomy, the left ureter is passed below the sigmoid mesentery to the right side of the pelvis. Both

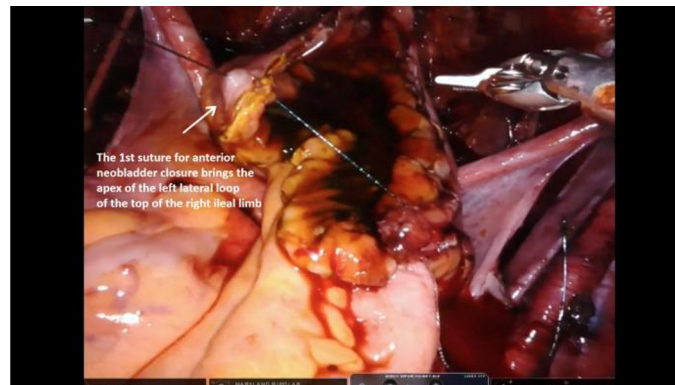


Figure 7. Anterior neobladder closure A.

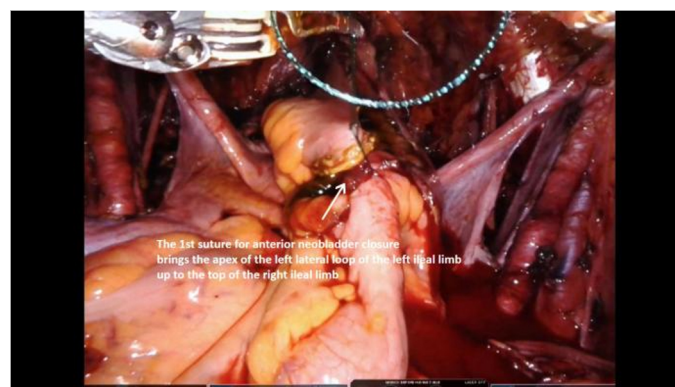


Figure 8. Anterior neobladder closure B.

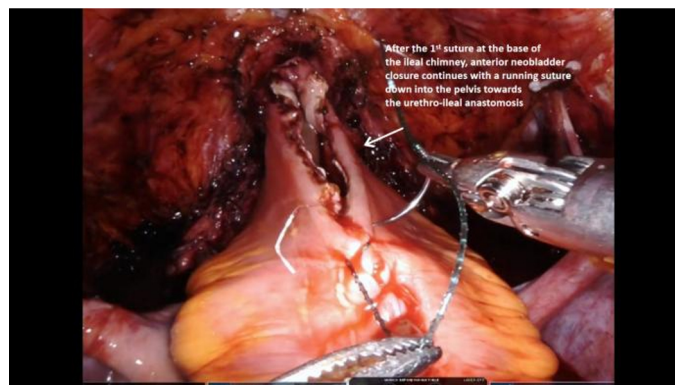


Figure 9. Anterior neobladder closure C.

ureters are then lifted vertically adjacent to each other, and the posterior plate of the Wallace anastomosis is done with an absorbable 4-0 monofilament suture [Figures 11-14]. A nephrostomy puncture needle is passed through the suprapubic area in the midline of the abdomen, through which both stents are passed [Figure 10]. Each one is then pulled through the opening in the anterior wall of the neobladder by the fourth arm, out through the ileal chimney, and inserted down each ureter. In keeping with the Wallace approach, the ureters are then anastomosed circumferentially with the open ileal chimney again using 4-0 absorbable monofilament suture, and the residual opening in the anterior wall of the neobladder is closed around the

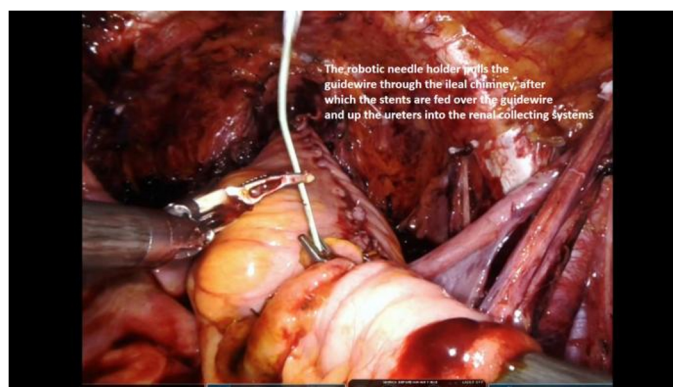


Figure 10. Stent insertion.



Figure 11. Posterior plate of Wallace uretero-ureteric anastomosis A.



Figure 12. Posterior plate of Wallace uretero-ureteric anastomosis B.

stents with 3-0 absorbable monofilament sutures [Figures 15-17]. Once closed, the neobladder reservoir can be tested for leakage by inflation with approximately 120 cc of normal saline injected through the 22 Fr urethral catheter [Figure 18].

Review of outcomes; evidence acquisition (see Tables 1-4 and Appendix 1)

To study comparative outcomes of RIN with respect to open intracorporeal neobladder, a literature search on OVID and EMBASE database was done while using keywords: robotic, cystectomy, intracorporeal

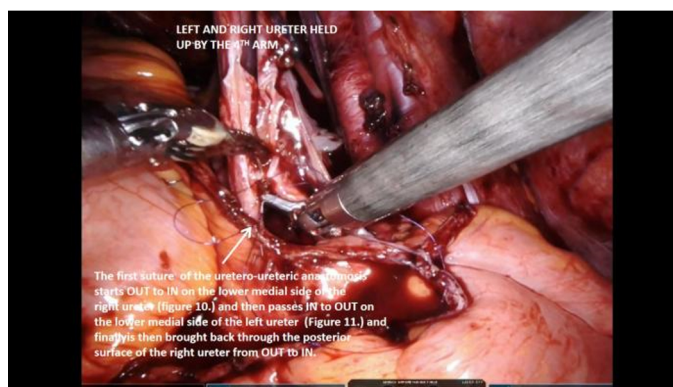


Figure 13. Posterior plate of Wallace uretero-ureteric anastomosis C.



Figure 14. Posterior plate of Wallace uretero-ureteric anastomosis D.

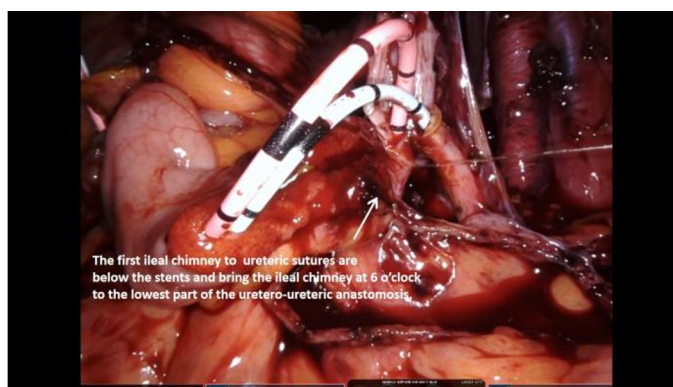


Figure 15. Ileo-ureteric anastomosis A.

neobladder, orthotopic, and intracorporeal urinary diversion. For evidence acquisition, inclusion and exclusion criteria are illustrated in Appendix 1. Inclusion criteria were original studies on RARC with RIN series, available in full text in English, published over the last 10 years, and with a specific analysis of oncological and functional outcomes. Overall, 10 studies were included and reviewed (see [Table 1](#)).

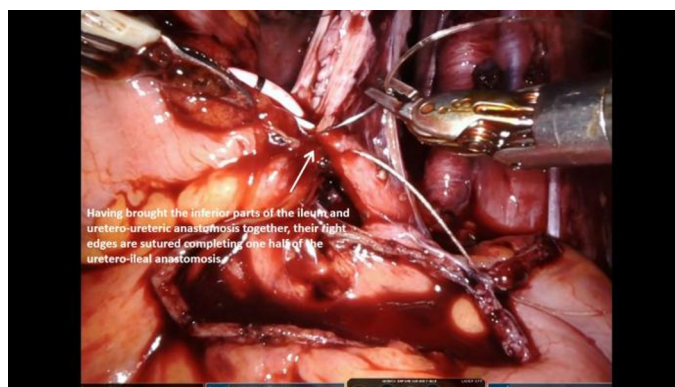


Figure 16. Ileo-ureteric anastomosis B.

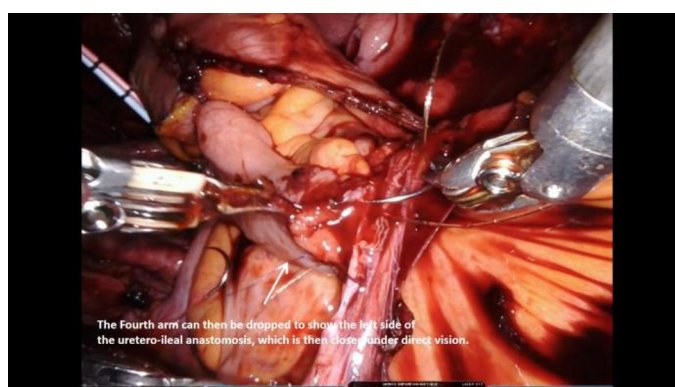


Figure 17. Ileo-ureteric anastomosis C.

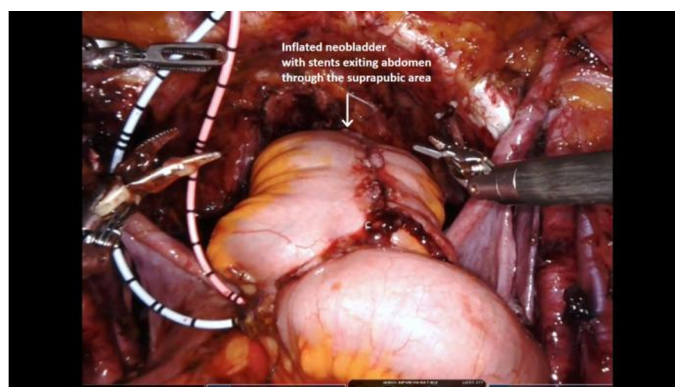


Figure 18. Inflation of neobladder.

RIN is the logical evolution of the minimally invasive approach for RARC, and it is recognized as its most technically challenging part. Moreover, most of the complications of the procedure are caused by this reconstruction. Studies focused on learning curves for RIN are discussed in more detail below, but, interestingly, it is not only operating times (OTs) that fall but also the rate of high-grade complications as centers gain experience^[5]. Although oncological outcomes data may seem more dependent on the cystectomy and extended lymph node dissection, the choice of RIN may also influence oncological outcomes by prolonged OTs or incomplete resection of tumor at the urethral margin. Nevertheless, apart

Table 2. Robotic intracorporeal neobladder study series: the oncological outcomes

Study	Number of patients had \leq pT2 (organ confined) postoperative in RIN	Number of patients had positive surgical margins in RIN	Lymph node yield (number)	Mean follow up (months) for cancer	Patients with the disease who are still alive at follow up	Est. Disease survival rate DSR% at 5 years	Est. Overall Survival rate OSR% at 5 years
Collins et al. ^[39] 2014	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Goh et al. ^[40] 2012	6	0	55	n/a	n/a	n/a	n/a
Hosseini et al. ^[5] 2020	129	2	23	34	114	70	71
Obrecht et al. ^[20] 2020	11	n/a	n/a	n/a	n/a	n/a	n/a
Tyritzis et al. ^[41] 2013	57	1	21	30	62	80.7	88.9
Desai et al. ^[42] 2014	109	1	29	25	95	71	72
Tuderti et al. ^[13] 2020	7	0	26	28	11	100	100
Schwentner et al. ^[43] 2015	38	4	23	37	52	76	71
Gu et al. ^[44] 2020	9	0	11	13	10	n/a	n/a
Jonsson et al. ^[23] 2011	35	1	19	25	31	84	n/a

RIN: Robotic intracorporeal neobladder.

Table 3. Robotic intracorporeal neobladder study series: the functional outcomes

Study	Number of patients had daytime continence*	Number of patients had nighttime continence	Number of patients achieved functional erection (not aided)	Mean follow up for continence (months)
Collins et al. ^[39] 2014	n/a	n/a	n/a	12
Goh et al. ^[40] 2012	6	n/a	n/a	3
Hosseini et al. ^[5] 2020	n/a	n/a	n/a	n/a
Obrecht et al. ^[20] 2020	12	9	n/a	6
Tyritzis et al. ^[41] 2013	48	40	12	12
Desai et al. ^[42] 2014	62	n/a	n/a	6
Tuderti et al. ^[13] 2020	10	9	8	12
Schwentner et al. ^[43] 2015	54	34	27	37
Gu et al. ^[44] 2020	9	8	2	6
Jonsson et al. ^[23] 2011	30	24	15	12

*Continence is defined as using 0-1 pads. Study excluded as follow up was less than 6 months. 73 patients only were followed for functional outcome.

Table 4. Robotic intracorporeal neobladder study series: result of pooled data analysis for all outcomes

Outcome	Median/Rate (interquartile range/calculation)
Peri-operative outcome	
Median OT (min) in RIN	435 (IQR = 57)
Median EBL (mL) in RIN	415 (IQR = 207.5)
Mean transfusion rate in RIN	8.73% (20/229)
Mean complication Clavien-Dindo \geq III rate at 30 days in RIN	20.25% (99/489)
Mean complication Clavien-Dindo \geq III rate at 90 days in RIN	13.39% (64/478)
Median length of hospital stay (days) in RIN	9 (IQR = 4.5)
Oncology outcome	
Mean Post-operative organ confined disease (\leq pT2) in RIN	80.04% (401/405)
Mean Positive surgical margins in RIN	1.86% (9/485)
Median lymph node yield (number)	23 (IQR = 7.5)
Mean follow up (months)	27.43 (range: 13-37)
Calculated mean cancer survival rate CSR%	77.96% (375/481)
Estimated median disease survival rate DSR%	78.35% (IQR = 13)
Estimated median overall survival rate OSR%	72% (IQR = 23.4)
Functional outcome (studies with follow up at least for 6 months)	
Mean daytime continence rate	81.52% (225/276)
Mean nighttime continence rate	61.08% (124/203)
Mean spontaneous sexual activity/potency rate	33.51% (64/191)

IQR: Interquartile range; RIN: robotic intracorporeal neobladder; OT: operating time; EBL: estimated blood loss.

from the obvious functional advantages, there is also the potential for less bowel manipulation, less blood and fluid loss, less hypothermia, and reduced ureteric trauma leading to lower ureteric stricture rates^[1,10,11]. Although a small proportion of patients in the reviewed series underwent intracorporeal ileal conduits, the overwhelming majority OF 87.5% had RARC with RIN.

Perioperative outcomes (see Table 1)

Less blood and fluid loss has been suggested as an advantage for ICUD. Prior figures from the recent IRCC analysis of ICUD vs. ECUD, of which 21% vs. 23% were neobladders, found less estimated blood loss (EBL) for ICUD at 300 mL vs. 350 mL and less transfusion at 5% vs. 13%. The median EBL of the series reviewed is 415 mL (IQR = 207.5), suggesting RIN may be associated with higher EBL compared to intracorporeal or extracorporeal ileal conduit. Where assessed, the transfusion rates in the series reviewed varied significantly from 4.2% to 66.7%, reflected in the variation in the numbers of patients and experience of the surgeons, and on pooled analysis, the transfusion rate is at 8.7%. For the larger series from established centers, transfusion rates for RIN (4.35% and 4.5%) are less than those quoted for ECUD in the IRCC data (13%)^[1]. Long OTs have contributed to complication rates and, with prolonged Trendelenburg position, may give rise to specific complications such as compartment syndrome or posterior infarction of the optic nerve. The combined OT of extended lymph node dissection, with additional nerve-sparing in men, or pelvic organ sparing in women will necessarily add to the duration of the procedure, sometimes breaching the recommended OT of the Pasadena Consensus Panel (PCP) of < 7 h^[12]. Nevertheless, the larger series from high-volume centers note a definite drop in OTs over the period of study, Hosseini *et al.*^[5] suggesting a plateau of approximately 5 h after 80 cases. Tuderti *et al.*^[13] performing an Intracorporeal Padua Ileal Neobladder with pelvic organ sparing RARC in women achieved a mean OT of 255 min. The median OT in Table 1 is 435 min (IQR = 57), just over the 7 h recommended by the PCP. Once again, the emphasis is on high volume centers with experienced surgical teams as well as standardization of the procedure to reduce OTs. Ninety-days high-grade complications rate from this series is 13.39%, ranging from 6% to 26%. It

compares favorably with the ICUD and ECUD high-grade complication rates (21% and 24% respectively) from the IRCC data^[1], as well as those of large open series from high volume centers^[14]. When analyzed, some RIN series found that high-grade gastrointestinal complications were particularly low, strongly supporting the suggestion that keeping the bowel intra-abdominally and reducing its manipulation is beneficial^[5].

Oncological outcomes (see Table 2)

The influence of RIN on oncological outcomes is important to establish, and it has been suggested to result from the pneumoperitoneum causing tumor seeding that changes the pattern of recurrence, the minimally invasive approach reducing lymph node yield, and possibly an increase in positive surgical margins with or without incomplete resection of tumor at the urethral margin^[15]. It has not been born out in the published results that have shown non-inferiority of RARC with RIN^[16,17], and this is further supported by the results of this review. In Table 2, the mean positive surgical margin of 1.86% (range 0%-6.4%), median lymph node yield of 23 nodes (IQR = 7.5), and mean cancer-specific survival rates of 78% (range 72%-100%) over mean follow up of 23.2 months (range 3-37 months) compares favorably with oncological outcomes from ORC and RARC with ECUD series^[18,19].

Functional outcomes (see Table 3)

While perioperative and oncological outcomes may be comparable for robotic and open approaches, naturally, the minimally invasive approach, analogous to potency and continence outcomes for robotic-assisted prostatectomy, may have the potential to demonstrate superiority in functional outcomes. The magnified view and dexterity afforded by robotic assistance may allow more accurate dissection around the pelvic floor with nerve and pelvic organ preservation, notwithstanding QoL improvements from a more physiologically functioning neobladder. The small study of Obrecht *et al.*^[20] (see Tables 1-3) examined functional outcomes after RARC with RIN over 12 months follow up including urodynamic measurements, bladder capacity, and a QoL assessment. Their results showed good functional outcomes with a median bladder capacity of 400 mL, which are close to the normal physiological bladder capacity and day continence rates of 100%^[20]. In this series, no patients required ISC, in keeping prior results of lower ISC rates for robotic neobladder than open neobladders^[21,22]. Similarly, from Table 3 in this review, the day continence rate is 81.5% (range 68%-100%) while the night continence rate is 61% (range 55%-82%), where continence was defined as using 0-1 pad. These results compare favorably to open neobladder series that demonstrate daytime and nighttime continence rates of 80%-100% and 45%-90% respectively^[22]. Generally, there is a paucity of potency or return to sexual activity outcome data in the literature after RIN. Jonsson *et al.*^[23] has reported potency of 88% of men who underwent RIN and nerve-sparing technique with potency defined as IIEF-5 ≥ 17 or the ability to perform intercourse. Tuderti *et al.*^[13]'s study focusing on female patients after pelvic organ sparing RARC with RIN, showed favorable functional outcomes with daytime and nighttime continence rates 90.9% and 86.4% respectively and 72% of patients returning to sexual activity at 12 months. Overall, for all series reviewed in Table 3, the mean potency or spontaneous return to sexual activity rate was 33.51% (range 16%-72%). Although some results may show a trend towards improved results for RIN, the claim of superiority of RIN over extracorporeal or open neobladder is difficult to make until results from better-designed studies support it^[24].

The early results of such studies are seen from Mastroianni *et al.*^[25], who recently reported an interim analysis from an ongoing randomized controlled trial between ORC vs. RARC with ICUD on Health-related Quality of Life after 1-year using patient-reported questionnaires from EORTC group, generic quality of life [QLQ-C30] and bladder cancer-specific instruments [QLQ-BLM30] questionnaires. Both approaches have comparable baseline QoL, as patients of two groups reported worsening physical

functioning, body image, and sexual functioning. The ORC group reported higher gastrointestinal symptoms of flatulence, irregular bowel habits, and abdominal bloating, which result in delayed return to normal daily activities and impaired role functioning (occupational, social, and financial roles), whereas patients who had RARC tend to experience more impairment of urinary symptoms and problems. Further results are expected with longer follow up reflected by urodynamic studies in both groups^[25].

Simone *et al.*^[26] assessed outcomes for prostate capsule and seminal vesicle sparing cystectomies to assess alternative techniques to improve the functional outcome. The results of 2-year follow-up on 20 patients who had organ-confined disease at TURB, negative urethral biopsy, and PSA < 4 ng/mL showed better continence and sexual function but worse oncological outcomes with a higher local recurrence rate of 20% and distant metastasis rate of 30%. It suggests a more traditional approach to nerve-sparing when dissecting the prostate, including excising the seminal vesicles with the prostate, may be a better technical approach when aiming to maximize functional outcomes^[26].

A summary of pooled analysis and outcomes of the series review is in [Table 4].

Trials

Evidence from recent trials has contributed to the outcomes debate. The RAZOR trial demonstrated that RARC is non-inferior to ORC for oncological outcomes, although the urinary diversion approach was extracorporeal in this trial. The two-year progression-free survival was 72.3% in RARC vs. 71.6% in ORC with no significant differences in lymph node yield, positive surgical margins, complication rates, or QoL assessments^[24]. The results of the iROC trial investigating RARC with ICUD (both ileal conduit and RIN) in comparison to ORC and ECUD are anticipated. For this study, participating surgeons must have completed at least 30 procedures of each, which will be close to the plateau of their learning curves. The study will report on oncological, perioperative, functional, and cost outcomes for RARC with ICUD and hopefully make a major contribution to the literature, potentially resolving some outstanding areas of doubt in the argument for RARC and ICUD vs. the open approach^[27].

Specific tips and tricks for the Karolinska modified Studer U bladder (see Table 5)

As has been highlighted, longer OR times may contribute to surgical trauma, influence postoperative complications, and mean prolonged Trendelenburg position, and negatively influence economics and cost analyses. Having a fastidious and reproducible step-by-step approach will allow smooth progression of the procedure and timely completion as well as faster progress up the learning curve for surgeons under mentorship. These tips and tricks highlighted in Table 5. aim to facilitate this process.

Economics

The question of economics is relevant to the widespread adoption of RARC and RIN as a form of urinary diversion. The intracorporeal orthotopic reconstruction may increase operative time but also has the potential to increase morbidity and complications, both of which may increase costs. Although the evidence is conflicting, and there may be institutional variation in cost-effectiveness, the general consensus is that RARC is more expensive than ORC^[28]. Using Prisma Methodology to select relevant studies, a recent review examined segmental costs to breakdown where the additional cost for RARC lies, examining the results from a total of 11 series. Operating costs, which included surgeon fees and occupation of the OR, both heavily dependent on OR time, accounted for 63.1%-70.5% of overall RARC costs, which will likely further increase with the addition of RIN^[28]. Interestingly, in an earlier study, Lee *et al.*^[29] highlighted differences in costs between Neobladder and Ileal conduit after RARC, finding RARC and ileal conduit had a cost advantage over ORC of \$4846, which was reversed to -\$1966 if neobladder was done. Of note, for this study, all urinary diversions were extracorporeal, although extrapolating this to RIN will likely exacerbate the

Table 5. Tips and tricks for robotic intracorporeal neobladder

Stage of operation	Tip	Challenge and possible complication	Figure
<i>Demarcation of the neobladder bowel segment</i>	Easier to bring down in women. Adhesiolysis of ileal segment, and possible division of mesentery taking care not to compromise blood supply may help to bring ileum down in difficult cases	Inability to bring the ileum into the pelvis may result in conversion to ileal conduit	Figure 1
<i>Urethro-ileal anastomosis</i>	Sub-urethral to ileal serosa Rocco type suture, to allow for tension-free urethro-ileal anastomosis	Without being tension-free, the anastomosis may break down, notwithstanding technical difficulty of suturing without losing its stabilizing effect	Figures 2 and 3
<i>Isolation of neobladder bowel segment and re-anastomosis of the bowel</i>	10 cm for right ileal limb and 40 cm for left ileal limb, which will consist of 10cm ileal chimney, and 20 cm left lateral ileal limb ^[4] .	Position of bowel that is re-anastomosed within right side of abdomen, and angle of stapler determined by fourth arm trocar position is important. Re-anastomosis is done by using 60 mm then 45 mm staples, then closed with final 60 mm staples. Anastomotic leak is a potential complication	Figure 4
<i>Detubularisation of the ileal neobladder limbs and formation of the posterior plate</i>	To set up closure of the posterior neobladder plate and the shape of the neobladder the position of 3 stay sutures is crucial Open the ileal lumen over suction tube	Opening ileal lumen over the suction tube helps prevent injury to posterior wall of the ileum. Judicious placement of 3 stay sutures limits technical difficulty of suturing posterior plate of the neobladder and eases later folding and anterior closure. Potential complications include injury to posterior ileal wall and posterior neobladder leak or rupture	Figures 5 and 6
<i>Anterior neobladder closure</i>	First suture from apex of left lateral limb to base of ileal chimney allows clear approach for anterior neobladder closure	Judicious suturing will prevent neobladder leak or rupture	Figures 7-9
<i>Stent insertion</i>	Using the seldinger technique, a venflon is inserted though the suprapubic area, and a guidewire is introduced, over which the stent is passed. Within the abdomen, a robotic needle holder is passed through the ileal chimney from top to bottom, ensuring the needle holder is closed to prevent injury to the chimney. Once it emerges from the bottom of the chimney, the guidewire is grasped, and pulled out through the tip of the chimney. The stent is passed over the guidewire and fed down the ureter. This process is repeated for right and left ureters	The robotic needle holder has to pass down the ileal chimney carefully to prevent injury, and later the stents must be pushed into the renal collecting system. They are sutured together to the skin of the anterior abdominal wall and removed at 14 days. They allow the uretero-ureteric and uretero-ileal anastomoses to heal, and help to prevent ureteric stricturing, anastomotic breakdown and leakage	Figure 10
<i>Uretero-ureteric anastomosis</i>	Both ureters are elevated in the right side of the abdomen using the fourth arm. The posterior ureteric plate is set up by the first suture, which is out to in on the lower medial side of the open right ureter, then in to out on the lower medial side of the left ureter, and then sutured. It is then brought back through the posterior surface of the right ureter from out to in. This opens up the posterior plate, so it is much easier to see the medial edges of each ureter. Finally, a running suture is passed superiorly closing the posterior surface of right to left ureters	The orientation of the suturing should be followed meticulously to allow efficient progress. Poor technique may cause anastomotic leakage and ureteric strictures	Figures 11-14
<i>Wallace uretero-ileal anastomosis</i>	The first ileal chimney to ureteric sutures is below the stents and brings the ileal chimney at 6 o'clock to the lowest part of the uretero-ureteric anastomosis. This allows closure of right side of ileal-ureteric anastomosis. The fourth arm can then be dropped to show the left side of the uretero-ileal anastomosis, which is then closed under direct vision	One of the most technically challenging parts of the procedures, and important at the beginning to keep sutures below the stents. Poor technique may cause anastomotic breakdown and leakage	Figures 15-17
<i>Completion of neobladder closure</i>	Following this the rest of the neobladder is closed around the stents and inflated to test for leakage	Judicious suturing to ensure tight closure. Potential complication is neobladder leak	Figure 18

difference in cost. The only study to date comparing RARC with intracorporeal urinary diversion with ORC is from the UK and examined 221 patients who underwent RARC, 7.7% of whom had RIN vs. 100 patients who had ORC, all of whom had ileal conduit^[30]. They found RARC 18.9% more expensive than ORC, primarily resulting from LOS and OTs, but also influenced by the volume of cases per annum. The influence of learning curves and surgeon experience is clear, and this would seem to support centralization from an economic point of view, such that larger high-volume centers will have shorter operating times, fewer complications, and lower robotic costs per case. Although it is reasonable to assume this applies to RARC with RIN, which exacerbates all the above, further studies are necessary to evaluate specific RIN case costs.

Learning curve

Because RIN is technically challenging, it would be fair to suggest this has impacted its more widespread adoption. In an attempt to standardize the learning, a number of studies have assessed the LC of RIN, a concept that has its origins in the aviation industry and training pilots^[31]. LC analysis aims to determine carefully chosen outcomes metrics to assess a learner's improvement, which in the context of RIN would include operative time, conversion rates, blood loss, complications rates, and LOS. Often studies have also included lymph node yield and surgical margin status, which may be more relevant to the EPLND and RARC. Nevertheless, embarking on learning this procedure does have advantages. Not only just the incorporeal approach, which keeps the bowel in the abdomen, reducing blood and fluid loss and hypothermia, minimizes surgical trauma and allows the bowel to recover quicker^[5] but also the inherent advantages of orthotopic neobladder with improved physical image and QoL, as well as better sexual function and continence in the majority of patients^[4]. In a recent LC analysis of 167 patients, with case numbers divided into tertiles to assess the impact of increasing case number on the defined outcomes (OR time, complications, LOS), Tuderti *et al.*^[32] found those patients operated on in the early part of the LC had worse perioperative and functional outcomes, which then normalized in later tertiles. Similarly, examining the first 100 consecutive cases of RARC and RIN, D'Annunzio *et al.*^[33] found an OR time plateau could be achieved at 20 cases, but 60 cases were required to achieve benchmark outcomes determined by the Pasadena RARC consensus. Earlier, Collins *et al.*^[34] examining a series of 67 patients that formed the first cases of a surgeon at a high-volume center, showed no compromise on perioperative and pathological outcomes. However, their study emphasized the importance of an experienced robotic mentor and team to supervise and guide the learning surgeon through these cases^[34]. This view is supported by Porreca *et al.*^[35], and using the analogy of LC analysis and educational research that has studied Robot-Assisted Radical Prostatectomy, a modern surgical approach to RARC and RIN. This approach would be multimodal, with didactic sessions, time to examine expert videos, and a highly structured modular approach to live operating under the close supervision of a mentor in a high-volume center, which will minimize any LC impact on both oncological and functional outcomes. Further studies with longer follow-up are needed to provide evidence for this viewpoint.

ERAS and RIN

ERAS programs' benefits and detailed protocols for patients undergoing RARC are well documented^[7] and were first described for colorectal patients in the late 1990s. Kehlett outlined a multimodal protocol of activities aimed at reducing the negative physiological and biochemical effects of surgical trauma to speed up postoperative recovery^[36]. Using a minimally invasive approach, RARC is synchronistic with this concept, and ERAS protocols have been beneficial^[7]. However, the combination of ERAS programs and robotic ICUD and specifically RIN has been less well studied. Tan *et al.*^[37] demonstrated that a detailed and well-applied ERAS program combined with intracorporeal urinary diversion could significantly reduce LOS and have a synergistic benefit on perioperative metrics without affecting 90-day complication and readmission risk, but out of 145 patients studied, only 11 underwent RIN. Similarly, Cerruto *et al.*^[38], in a series of 31 patients having combined RC and Neobladder, demonstrated reduced complications in the

postoperative period, but the surgery was not performed robotically. There are a number of studies examining ERAS in RARC, but only a small number of these include RIN, and although it is perceptively that the combination would be beneficial, more study is required^[7].

CONCLUSION

There has been slow adoption of RARC with RIN in specialized centers for the treatment of high-risk and muscle-invasive bladder cancer. Although it is a challenging technique, it represents a natural evolution of the minimally invasive approach with robotics. The technique has a steep LC and longer OTs as a result and many potential advantages, such as less bowel manipulation, less fluid and blood loss, and quicker return of bowel function. Larger retrospective series with longer follow up are beginning to emerge, but there remains significant heterogeneity in the experience of the teams and surgeons involved, making meaningful interpretation of their results challenging. Nevertheless, from higher volume centers, results demonstrate the safety and feasibility of RARC with RIN. Perceptively, perioperative and functional outcomes for well-selected patients may be superior to ileal conduit and ECUD. However, the results of well-structured studies such as the iROC are keenly anticipated and will hopefully shed light on some of these unanswered questions.

DECLARATIONS

Authors' contributions

Performed data analysis, interpretation, and manuscript write up: Maqboul F

Technical description of operative steps, data acquisition: Dovey Z

Review of manuscript: Thinagaran JKR

Review and substantial contributions to conception and design of study: Dovey Z, Wiklund P

Availability of data and materials

Not applicable.

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Conflicts of interest

Dr. Zach Dovey is Medical Director and stock owner (with certificate of shares) of Medtech Holdings Ltd.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Original Article

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Predictors of re-intervention after greenlight laser photoselective vaporization of the prostate: multicenter long/mid-term follow-up experience

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Abstract

Aim: Greenlight photoselective vaporization of the prostate (PVP) is considered a safe alternative to transurethral resection of the prostate (TURP) in men with lower urinary tract symptoms (LUTS) and a prostate volume of 30-80 mL for the comparable short- and mid-term results. Long-term re-treatment rate is still being debated.

Methods: We retrospectively reviewed greenlight PVP procedures in a multi-institutional database from September 2011 to December 2019 collecting data on patients requiring re-intervention with a follow-up period of at least 12 months.

Results: Among 867 patients with a median follow-up period of 32.5 months (interquartile range: 20.0-49.0 months), 35 patients (4%) required re-intervention. Patients requiring re-intervention had a prostate volume ≥ 100 mL in 28.6% of cases ($P = 0.002$). Preoperative urethral stricture and incidence of early complications were more frequent in the re-treatment group ($P = 0.027$ and $P = 0.006$). In the re-treatment group, 22 patients required an endoscopic intervention for bladder neck or prostatic fossa contracture (2.5% of the study population). The remaining 13 patients in the re-treatment group underwent TURP or PVP for LUTS relapse (1.5%). In the univariate and multivariate logistic regression models, only prostate volume ≥ 100 mL ($P = 0.003$ and $P = 0.010$), preoperative urethral stricture ($P = 0.013$ and $P = 0.036$), and occurrence of early complications ($P = 0.008$ and $P = 0.024$) correlated with re-intervention.

Conclusion: Greenlight PVP has good functional long/mid-term results. The presence of preoperative urethral stricture and the occurrence of early complications correlate with the risk of late re-treatment. In patients with prostate ≥ 100 mL, the enucleation technique may be superior to vaporization in terms of lower long-term risk of re-intervention for LUTS relapse.

Keywords: Greenlight laser, long-term results, re-intervention

INTRODUCTION

Benign prostatic obstruction (BPO) causing lower urinary tract symptoms (LUTS) is present in up to 80% of men over the age of 80 and in up to 50% of men over the age of 50, resulting in significant economic burden and potentially negative impact on the quality of life^[1]. Pharmacological management with alpha 1-blockers or combination therapies (alpha 1-blockers + 5-alpha-reductase inhibitors or alpha 1-blockers + muscarinic receptor antagonists) is the first-line treatment. Surgical treatment is indicated in the case of pharmacological management failure or discontinuation^[2-4]. Nowadays, despite the availability of several laser technologies (holmium, greenlight, diode, and thulium), monopolar or bipolar transurethral resection of the prostate (M- or B-TURP) is considered the first-line treatment for patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL, due to the absence of long-term surgical randomized controlled trials on laser treatments^[2]. The longer catheterization time and hospital stay, with a higher risk of hemorrhagic complications in transurethral resection of the prostate (TURP) series in comparison to laser series^[5], are increasing the use of lasers in the treatment of BPO. Some limitations preventing further spreading of holmium laser enucleation of the prostate (HoLEP) and thulium vapoenucleation of the

prostate (ThuVEP) are a long learning curve and the need for further materials regarding morcellation. The 180-W LBO crystal Green Light Xcelerated Performance System (XPS)TM (American Medical System-AMS, Minnetonka, Minnesota) and the new 532 nm wavelength, metal-capped and liquid cooled irrigated fiber (Moxy TM fiber) with its different and versatile uses [standard photovaporization (PVP), anatomical PVP, and greenlight enucleation of prostate (GreenLEP)] have allowed us to overcome these drawbacks^[6,7]. Current guidelines consider greenlight laser as an alternative to TURP in men with moderate-to-severe LUTS and a prostate volume of 30-80 mL, in light of their comparable short- and mid-term results^[3,7]. Moreover, some evidence is emerging supporting the use of greenlight laser also for large volume prostates and in men on anticoagulation or with high cardiovascular risk^[8-11]. According to the current literature, the major limitation of greenlight is the absence of long-term follow-up (≥ 36 months) data to evaluate the outcome, the rate of re-intervention, and patient satisfaction. For these reasons, we decided to review and update our large multicenter cohort of patients who have undergone greenlight laser treatment in order to analyze the long-term re-treatment rate and risk factors for treatment failure.

METHODS

We retrospectively reviewed all cases undergoing standard or anatomical greenlight laser photoselective vaporization of the prostate for lower urinary tract symptoms secondary to BPO, using the 180-W XPS GL system, in a multi-institutional, prospectively collected database performed in 20 Italian centers from September 2011 to December 2019, and collecting data on patients developing LUTS relapse requiring re-intervention (TURP or greenlight PVP) with a follow-up period of at least 12 months. Surgeons with consolidated experience in greenlight PVP performed all considered procedures. Informed consent was obtained from all individual participants included in the study. This study was approved by the institutional research ethical committee and all related procedures were conducted in accordance with the Declaration of Helsinki. Patients with all the following data were considered in the statistical analysis: age, prostate volume evaluated with trans-rectal ultrasound (TRUS), use of antiplatelet and anticoagulant medications, LUTS therapy and history of catheterization or retention, PSA level, IPSS, maximum urinary flow (Qmax), operative time, lasing time, catheterization time, hospital stay, and complications. The Clavien-Dindo classification was used to describe reported complications and divided into early (30 days) or late (> 30 days) complications^[12,13]. Postoperative frequency and urgency were considered as complications when they prompted additional medical examination or when reported by patients affecting the Patient Global Impression of Improvement scale (PGI-I)^[14]. The presence of any degree and type of incontinence (stress or urge incontinence) reported by the patients and impairing their quality of life was defined as urinary incontinence. All patients underwent an outpatient clinic evaluation after at least 6 and 12 months and then annually with IPSS, Qmax, PSA level, and the PGI-I scale. Follow-up was calculated as the time from surgery to the last visit. Patients with a history of prostate cancer, neurogenic bladder disease, and previous prostate surgery, as well as those who underwent GreenLEP or contemporary treatment of bladder stones, including incidental bladder tumors, were not considered in this study.

Statistical analysis

Quantitative variables were summarized as median and interquartile range (IQR). Qualitative data were summarized as frequency and percentage. After stratification according to reintervention performance, the Chi-square and the Mann-Whitney *U* tests were used to test the statistical significance in proportions and median differences. We relied on univariable and multivariable logistic regression models to test main predictors of reintervention. Multivariable logistic regression models included covariates that were statistically significant at univariable analysis. All tests were two-sided, and the level of statistical significance was set at $P < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 4.0.5; <http://www.r-project.org/>).

Table 1. Values are n (%) or median interquartile range. Patients' preoperative and intraoperative characteristics

	No re-intervention n = 832	Re-intervention n = 35	Overall n = 867	P value
Age (years)	68.0 (63.0-75.0)	70.0 (64.0-74.0)	68.0 (63.0-75.0)	0.696
Prostate volume, TRUS (mL)	60.0 (45.0-75.0)	65.0 (45.0-100.0)	60.0 (45.0-75.5)	0.236
Antiplatelet/anticoagulant therapy				0.535
None	485 (58.3%)	20 (57.1%)	505 (58.2%)	
Antiplatelet	239 (28.7%)	9 (25.7%)	248 (28.6%)	
Anticoagulant	91 (10.9%)	4 (11.4%)	95 (11.0%)	
Unknown	17 (2.0%)	2 (5.7%)	19 (2.2%)	
BPH/LUTS therapy				0.808
None	131 (15.7%)	6 (17.1%)	137 (15.8%)	
Alpha-blockers	404 (48.6%)	19 (54.3%)	423 (48.8%)	
5-ARI	48 (5.8%)	1 (2.9%)	49 (5.7%)	
Combination	249 (29.9%)	9 (25.7%)	258 (29.8%)	
Indwelling catheter history	118 (14.2%)	9 (25.7%)	127 (14.6%)	0.059
Operative time (min)	55.0 (40.0-75.0)	55.0 (40.0-65.0)	55.0 (40.0-75.0)	0.778
Lasing time (min)	25.0 (18.0, 34.0)	24.0 (17.0, 38.0)	25.0 (18.0, 34.0)	0.978
Catheterization time (days)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.841
Postoperative stay (days)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.529
Early complications	352 (42.3%)	23 (65.7%)	375 (43.3%)	0.006

TRUS: Trans-rectal ultrasound; LUTS: lower urinary tract symptoms; 5-ARI: 5 alpha-reductase inhibitors.

RESULTS

Among 885 patients with at least 12 months of follow-up, 18 patients with postoperative urethral stricture (2%) were excluded from the analysis. In total, 867 patients with a follow-up of at least 12 months and all the required data for inclusion were considered for analysis. With a median follow-up period of 32.5 months (IQR: 20.0-49.0 months), 35 patients (4%) required re-intervention for LUTS relapse in our database. All preoperative data are reported in Table 1. The median prostate volume of the study population was 60.0 mL (IQR: 45.0-75.5 mL), including 102 patients (11.8%) with a prostate volume ≥ 100 mL. No statistical differences were found between the two groups in terms of age, use of antiplatelet and anticoagulant medications, LUTS therapy, and history of catheterization or retention [Table 1]. Patients requiring re-intervention had a prostate volume ≥ 100 mL in 28.6% of cases *vs.* 11.1% in the no re-treatment group ($P = 0.002$). Interestingly, preoperative urethral stricture was more frequent in patients undergoing re-intervention (17.1% *vs.* 6%, $P = 0.027$). Intra- and peri-operative data were similar; however, patients requiring reoperation had a higher incidence of early complications [Table 1]. Despite the higher incidence of early complications in the re-treatment group, the type of complications was similar between the two groups [Table 2]. The three most frequent early complications in the treatment failure group and the no re-treatment group were burning urination (25.7% and 15.3%), urgency (17.1% and 11.5%), and postoperative urinary retention (14.3% and 8.5%). In addition, the incidence of late complications was higher in the re-intervention group, as reported in Table 2. In the re-intervention group, 22 out of 35 patients (62.8%) required a surgical endoscopic intervention for *de novo* lower urinary tract symptoms linked to bladder neck or prostatic fossa contracture. In particular, bladder neck and prostatic fossa contracture were more frequent in the patient group undergoing re-intervention (37.1% *vs.* 0.7% and 25.7% *vs.* 0.6%, respectively, $P < 0.001$). Contrariwise, no patients required surgical intervention for these complications in the control group because these did not affect urodynamic patterns. In fact, the Qmax and the PGI-I were better in patients not requiring re-intervention [Tables 2 and 3]. The remaining 12 patients (1.4% of the study population) in the re-treatment group underwent a second PVP or a TURP for LUTS relapse after surgery.

Table 2. Type of complications

Complications	Clavien-Dindo grade	No re-intervention n= 832	Re-intervention n = 35	Overall n = 867	P value
Perioperative					
Prostatic capsule perforation	IIIa	6 (0.7%)	0 (0.0%)	6 (0.7%)	0.614
Early (< 30 days)					
Fever < 38 °C	I	15 (1.8%)	1 (2.9%)	16 (1.8%)	0.650
Fever > 38 °C	I	23 (2.8%)	1 (2.9%)	24 (2.8%)	0.974
Burning urination	I	127 (15.3%)	9 (25.7%)	136 (15.7%)	0.096
Frequency	I	66 (7.9%)	2 (5.7%)	68 (7.8%)	0.633
De novo urge	I	96 (11.5%)	6 (17.1%)	102 (11.8%)	0.313
Urge incontinence	I	54 (6.5%)	4 (11.4%)	58 (6.7%)	0.252
Stress incontinence	I	38 (4.6%)	3 (8.6%)	41 (4.7%)	0.274
Hematuria	I	24 (2.9%)	1 (2.9%)	25 (2.9%)	0.992
Retention	I	71 (8.5%)	5 (14.3%)	76 (8.8%)	0.238
UTI	II	10 (1.2%)	1 (2.9%)	11 (1.3%)	0.391
Blood transfusion	II	4 (0.5%)	0 (0.0%)	4 (0.5%)	0.681
MACE	IVb	6 (0.7%)	1 (2.9%)	7 (0.8%)	0.167
Late complication					
Stress incontinence	I	26 (3.1%)	1 (2.9%)	27 (3.1%)	0.929
Bladder neck/prostatic fossa contracture requiring reintervention	IIIb	0 (0%)	22 (62.8%)	22 (2.6%)	< 0.001
BPH recurrence requiring surgical reintervention	IIIb	0 (0%)	13 (37.2%)	13 (1.4%)	< 0.001
Patient global impression of improvement					
I		401 (51.5%)	11 (34.4%)	412 (50.9%)	
II		291 (37.4%)	11 (34.4%)	302 (37.3%)	
III		62 (8.0%)	6 (18.8%)	68 (8.4%)	
IV		16 (2.1%)	3 (9.4%)	19 (2.3%)	
V		5 (0.6%)	0 (0.0%)	5 (0.6%)	
VI		3 (0.4%)	1 (3.1%)	4 (0.5%)	

Interestingly, there were no differences in PSA changing and IPSS between the two groups at the follow-up visit [Table 3]. At the univariate and multivariate logistic regression models only prostate volume ≥ 100 mL ($P = 0.003$ and $P = 0.010$), preoperative urethral stricture ($P = 0.013$ and $P = 0.036$), and occurrence of early complications ($P = 0.008$ and $P = 0.024$) were associated with re-intervention [Table 4].

DISCUSSION

Despite the great interest in greenlight treatment for BPO, few data are available on long-term follow up and even fewer on failure predictors. These aspects depend on the novelty of this technology. The last development of greenlight was the 180-W XPS launched in 2010. The Goliath Trial, designed at the beginning of the greenlight 180-W XPS experience in 2011, with 128 patients and 2 years of follow-up, described non-inferiority compared to TURP, with 9% re-treatment rate vs. 7.6% in the TURP group^[15]. In this study, the mean prostate volume was 48.6 ± 19.2 mL. However, these data have been overcome by some retrospective papers. Ajib *et al.*^[16] described a re-intervention rate of 2.6% at 12 months for bladder neck contracture and a re-intervention for LUTS relapse of 0.5%, 0.7%, and 4.8% at 12, 24, and 48 months, respectively. In a previous paper from our database, we reported 24 patients out of 813 (3.1%) requiring re-intervention with a median follow-up period of 17.7 months (IQR: 12-25.8 months)^[17].

Table 3. Main outcomes after photoselective vaporization of the prostate

Outcome	Baseline	6 months	12 months
PSA ng/mL, median (IQR)			
No re-intervention (n = 832)	2.7 (1.6-3.9)	1.3 (0.7-2.1) (n = 439)	1.2 (0.7-2.0) (n = 501)
Re-intervention (n = 35)	2.4 (1.3-4.3)	2.0 (0.7-3.7) (n = 10)	1.3 (0.6-3.6) (n = 17)
Overall (n = 867)	2.6 (1.6-3.9)	1.3 (0.7-2.1) (n = 449)	1.2 (0.7-2.0) (n = 518)
P value	0.767	0.346	0.647
Qmax mL/s, median (IQR)			
No re-intervention (n = 832)	8.7 (7.0-10.9)	19.4 (16.6-24.0) (n = 650)	19.8 (16.9-24.0) (n = 533)
Re-intervention (n = 35)	7.0 (5.0-9.8)	18.0 (16.0-20.9) (n = 21)	18.0 (14.4-19.5) (n = 19)
Overall (n = 867)	8.7 (7.0-10.6)	19.4 (16.0-23.5) (n = 671)	19.6 (16.5-23.8) (n = 552)
P value	0.012	0.048	0.004
IPSS, median (IQR)			
No re-intervention (n = 832)	23.0 (19.0-27.0)	7.0 (5.0-10.0) (n = 624)	5.0 (3.0-8.0) (n = 539)
Re-intervention (n = 35)	23.5 (20.0-27.8)	8.0 (6.2-10.0) (n = 26)	5.0 (4.0-8.0) (n = 23)
Overall (n = 867)	23.0 (19.0-27.0)	7.0 (5.0-10.0) (n = 650)	5.0 (3.0-8.0) (n = 562)
P value	0.457	0.129	0.603

IQR: Interquartile range; Qmax: maximum urinary flow.

Table 4. Univariate and multivariate logistic regression

	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95%CI)	P value
Age	1.00 (0.96-1.05)	P = 0.843	-	-
Prostate volume ≥ 100	3.22 (1.43-6.73)	P = 0.003	2.77 (1.22-5.86)	P = 0.010
Antiplatelet/anticoagulant therapy	0.90 (0.44-1.79)	P = 0.765	-	-
BPH/LUTS therapy				
None	-	-	-	-
Alpha-blockers	1.03 (0.42-2.87)	P = 0.956	-	-
5-ARI	0.45 (0.02-2.76)	P = 0.471	-	-
Combination	0.79 (0.28-2.40)	P = 0.660	-	-
Indwelling catheter history	2.09 (0.91-4.42)	P = 0.064	-	-
Preoperative urethral stricture	3.24 (1.17-7.67)	P = 0.013	2.74 (0.97-6.63)	P = 0.036
Early complications	2.61 (1.31-5.50)	P = 0.008	-	-

LUTS: Lower urinary tract symptoms; 5-ARI: 5 alpha-reductase inhibitors.

In this further analysis of our updated, multicenter experience, the rate of re-intervention for bladder neck contracture or LUTS relapse is 4% (35 out of 867 patients) with longer follow-up (median, 32.5 months, IQR: 20.0-49.0 months; minimum, 12 months). In detail, only 1.4% (12 patients) underwent a second PVP or a TURP for LUTS relapse. Recently, the Global Greenlight Group published data from 3627 patients who

underwent greenlight PVP with a median follow-up of 6 months, and the authors reported a re-treatment rate of 1.5% and an incidence of bladder neck contracture of 1.93% in 569 patients at 5-year follow-up^[8], in line with our results. Unfortunately, in all cited articles, the authors performed only a descriptive analysis, without analyzing risk factors for treatment failure. In our database analysis, apart from a descriptive analysis of results, we analyzed the possible risk factors of treatment failure after greenlight PVP. In the univariate and multivariate logistic regression models, three factors correlated with re-intervention: preoperative urethral stricture ($P = 0.013$ and $P = 0.036$), incidence of early complications ($P = 0.008$ and $P = 0.024$), and prostate volume ≥ 100 mL ($P = 0.003$ and $P = 0.010$) [Table 4]. The correlation between the incidence of early complications (burning urination, urgency, and urinary retention) and the risk of re-treatment due to LUTS relapse may correlate with inefficacious vaporization due to inadequate adenoma removal with excess energy absorption by the prostatic tissue, a factor which might have an inflammatory and irritating effect. Obviously, this is a hypothesis not confirmed by our data in this analysis. In fact, operative and lasing time as well as PSA changing at 12 months are similar in the two groups ($P = 0.778$, $P = 0.978$, and $P = 0.674$, respectively). However, in a recent paper of our group, where we analyzed risk factors of postoperative acute urinary retention after greenlight laser procedures, lower lasing time, adenoma volume < 40 mL, IPSS ≥ 19 , and 5 alpha-reductase inhibitors (5-ARI) assumption were associated with a higher risk of postoperative acute urinary retention, implying that an inefficacious vaporization and an inflammatory component may play a role^[18].

A further evaluation is necessary for patients with prostate volume ≥ 100 mL. In a recent analysis of ours regarding functional results in patients with large prostate volume, the re-intervention rate in the ≥ 100 mL group was 3.5% vs. 2.3% in the group with prostate volume < 100 mL with a mean follow-up of 25.0 months (IQR: 16.5-35.0 months)^[10]. In the literature, the re-intervention rate of patients undergoing greenlight PVP for large prostate volume is reported as 15.2% by Laine-Caroff (with a median follow-up of 54 months)^[19], 13.2% by Meskawi *et al.*^[20], 6% for 200 mL prostate and 9% for 100-200 mL in a multi-institutional series^[21], 2.9%^[22], 1.2%^[23], and no re-treatment at 12 months reported by Altay *et al.*^[24]. In these papers, larger prostate volume, low energy density, and a lower PSA reduction at 6 months after surgery^[20] or low energy density^[23] are reported as risk factors for treatment failure.

Despite the good functional results associated with low morbidity, in these vaporization series, a large prostate is a consideration which should be made concerning the enucleation technique. In a recent nationwide database, including 58,346 patients (38,308 TURP and 20,038 HoLEP), the authors reported a higher reoperation rate in the TURP group (4.50%) than in the HoLEP group (1.27%) ($P < 0.01$) with mean follow-up durations of 51.6 and 47.6 months, respectively^[25].

These data are in line with a randomized trial comparing greenlight PVP vs. B-TURP vs. HoLEP in large prostate (80-150 mL), with 3 years of follow-up and a re-treatment rate of 6.7%, 9.7%, and 0%, respectively^[26]. The authors postulated that pure enucleation may guarantee longer functional results than vaporization or resection techniques. The experience in GreenLEP reported by Ferrari *et al.*^[27] with a study population of 120 patients, a median prostate volume of 98.5 mL (IQR: 83.0-130.0 mL), and a median follow-up of 18 months seems to go in this direction, with no reoperation. Obviously, more studies are needed to confirm this finding.

Some limitations are present in our study, the first being the retrospective nature and the participation of 20 centers. An additional issue to be taken into consideration is the absence of enucleation procedures. Nevertheless, the follow-up period is one of the longest in the literature. In our experience, the re-treatment rate of 1.4% and the 2.6% rate of bladder neck contracture requiring endoscopic revision after a median of

23 months postoperatively are in line with results from other greenlight and TURP series. Prostate volume \geq 100 mL, preoperative urethral stricture, and the early-onset complications correlate with the re-treatment risk. Greenlight PVP has good functional long/mid-term results. The presence of preoperative urethral stricture and the occurrence of early complications correlate with the risk of late re-treatment. In patients with prostate \geq 100 mL, the enucleation technique may be superior to vaporization in terms of lower long-term risk of re-intervention for a LUTS relapse.

DECLARATIONS

Authors' contributions

Conception and design: Campobasso D, Cindolo L

Data acquisition: Greco F, De Nunzio C, Destefanis P, Varvello F, Reale G, Cai T, Malossini G, Oriti R, Tuccio A, Ruggera L, Laganà A, Dadone C, De Rienzo G, Pucci L, Montefiore F, Rabito S, Germani S

Data analysis and interpretation: Campobasso D, Marchioni M, Cindolo L

Drafting the manuscript: Campobasso D, Cindolo L

Critical revision of the manuscript for scientific and factual content: Greco F, De Nunzio C, Ferrari G

Statistical analysis: Marchioni M

Supervision: Destefanis P, Fasolis G, Voce S, Cai T, Ruggera L, Tubaro A, Dadone C, Gontero P, Carrino M, Miano R, Schips L, Frattini A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflict of interest

Destefanis P, Ruggera L, Dadone C, Ferrari G and Cindolo L do surgical tutorship for American Medical System and received honoraria for their tutorship.

Ethical approval and consent to participate

Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

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Systematic Review

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Functional and oncological outcomes with male nerve sparing robotic assisted radical cystectomy

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Abstract

Aim: In keeping with the ethos of surgical oncology, male nerve sparing (NS) robotic assisted radical cystectomy (RARC) aims to maximise functional outcomes without sacrificing oncological outcomes. This review details the surgical technique of male NS RARC as well as discussing strategies that may be employed in tandem with surgery to improve post-operative recovery and longer-term quality of life.

Methods: An OVID/EMBASE database search was done with key words of robotic, cystectomy, male and nerve sparing. Publications with no description of post-operative functional outcome were excluded. A total number of 25 relevant publications were selected investigating male NS RARC, assessing functional outcomes along with other surgical standard indicators.

Results: Most series contained small numbers of patients with largely retrospective data and the associated bias of selection. Mean follow up of 27.06 months (range 2.8-58 months) was noted overall. Study design, technique, definitions and measurements of continence and erectile function are heterogeneous across series. With a mean follow up of 27.06 months (range 2.8-58 months), a post-operative satisfactory erectile function of 54.32% (range 9%-100%) and satisfactory day time continence of 90% (range 54.5%-100%) and night time continence of 80.55% (range 46.7%-88%) was found with a mean positive surgical margin rate of only 1.8% (range 0%-6.4%).

Conclusion: Male NS RARC for appropriately selected patients will offer good functional outcomes. Results from the series reviewed suggest the technique is both feasible and safe, without compromising longer term oncological results.



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Keywords: Nerve-sparing, robotic, cystectomy, functional outcomes, continence, erection

INTRODUCTION

Over 1.72 million people worldwide live with bladder cancer (BC), half of them are from the North America and Europe and men are affected about 4 times more than women^[1]. BC accounts for the highest lifetime treatment cost per patient among all cancers, with the United States spending €3.6 billion^[2] and Europe another €5 billion^[3] per year on the investigation and management of BC. Though there is a decreasing trend in tobacco use in many parts of the world, overall population growth and increasing longevity has led to a rise in BC incidence^[4], which shows no signs of abating.

Muscle invasive BCs and occasionally high-grade superficial BCs are managed surgically by radical cystectomy. This is a morbid operation with prolonged recovery time and complications that may be long lasting in some patients. Nevertheless, radical cystectomy has evolved greatly over the years with improvement in knowledge, skills and technology. Marshall and Whitmore^[5] provided the first detailed description of a radical cystoprostatectomy and pelvic lymph node dissection in 1949. After Clayman performed the first laparoscopic nephrectomy in 1991, a minimally invasive approach was promoted by urologists for various procedures. More complicated operations like prostatectomy were also performed laparoscopically, but minimally invasive surgery really came into its own when the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) came into play^[6]. With the advent of robotic assistance in urology and the emergence of robotic assisted radical cystectomy (RARC), allowing better dexterity and visibility, the boundaries have been pushed and expectations have improved.

Although there are similarities in some of the basic technical aspects of nerve sparing (NS) for a radical prostatectomy and a radical cystectomy, there are also some key differences; notwithstanding the potential for urothelial cancer to be more lethal than prostate cancer. This makes patient selection for NS in RARC particularly important. However, there is a reasonable body of evidence establishing the short term (≤ 5 years) oncologic safety of performing a NS operation for bladder cancers^[7,8], which has encouraged Uro-Oncologists to increase the application of this approach in their practice. This review aims to study the technique of male NS RARC, review the results now available in the literature, and examine the status of their functional outcomes and survival outcomes with longer term follow up. Before this, the neuroanatomy of the pelvic plexus will be discussed to provide an understanding of how the technical approach to NS during RARC has developed.

METHODS

Neuroanatomy of the pelvic plexus

The neuroanatomy of the pelvic plexus was originally described in a landmark paper by Walsh and Donker^[9] in 1982, studying nerves that supply the penis and pelvic organs in males stillborn at birth. Sympathetic input to pelvic plexus arises from T11-L2 and stimulates ejaculation as well as increasing the bladder neck and urethral tone by inducing contraction of the smooth musculature. Parasympathetic input arises from S2-4 with fibres joining the pelvic plexus and controlling bladder muscle contraction and erectile function. Nerve fibres originating from the pelvic plexus are generally unmyelinated^[10]. Tewari further described the surgical neuro-anatomy of the pelvic plexus, dividing it into three distinct zones, that all may be injured during dissection, and thus cause postoperative erectile dysfunction^[11]. In broad terms the plexus lies in the subperitoneal tissue near the pelvic ureter and its relation to the vas deferens, and extends forward in a rectangular shape over the lateral and posterior parts of the seminal vesicles (SVs). Its three surgically distinct zones include the proximal neurovascular plate (PNP), containing the cell bodies of the

pelvic plexus, which is in close proximity to the SVs as above, the predominant neurovascular bundle (PNVB) in the groove between posterolateral prostate and rectum, and the accessory nerve pathways (ANPs) on the lateral surface of the prostate in the lateral prostatic fascia^[10,11]. During surgical dissection, injury caused by direct trauma or cautery, inflammation, or ischaemia to any of the nerve fibres is potentially reversible, but cell body injuries are not. The pudendal nerve, with somatic cell fibres from Onuf's nucleus in the anterior horn of S2-4, supplies the pelvic floor muscles and external sphincter. In the context of male NS RARC, this is relevant to neobladder operations, where injury to its nerve branches when dissecting and ligating the dorsal vein complex, may compromise post-operative continence^[10]. A detailed knowledge of the neuroanatomy will provide the operating surgeon with direction when dissecting around the SVs, base of prostate and distally towards the prostatic apex, in order to achieve the most effective NS whilst proceeding through the steps of RARC described below.

Patient preparation and selection

Patient selection is crucial to surgical planning, especially for the NS approach, with some basic contraindications when considering the RARC part as well as more specific criteria for NS. Moreover, the decision to proceed with NS may be made in conjunction with consideration for orthotopic neobladder, which will also require specific criteria for patient selection. Generally, depending on the surgeon's experience, relative contraindications to RARC would include BMI > 35, severe vasculopathy with a history of surgery, severe cardiorespiratory illness, prior pelvic trauma, surgery or radiation, and locally advanced disease^[12]. For male NS, preoperative potency is a basic requirement, with a desire for ongoing sexual activity postoperatively. Some studies have suggested an age cut off of 65 years, based on poorer recovery in older age groups^[13], but if patients have reasonable preoperative potency, and otherwise are suitable for selection, age should not be a factor in the decision-making process. Positive surgical margin rates have been noted to rise with increasing tumour stage^[14], and clinical tumour stage should be T2 or less. Some groups also suggest clinical evidence of prostate cancer should be a contraindication^[15], but if this has been proven as localized or low volume intermediate risk prostate cancer by preoperative prostate biopsy and multiparametric Magnetic Resonance Imaging prostate, NS may still be undertaken. If orthotopic neobladder is also being considered, patients require unimpaired renal and liver function, no history of urethral sphincter injury, the necessary motivation and cognitive function to undertake the postoperative neobladder training protocols as well as the dexterity to perform intermittent self-catheterization^[16].

Preoperative preparation for patients in modern robotic centres will include application of enhanced recovery after surgery (ERAS) protocols, as well as advice regarding preoperative lifestyle changes and physical activity in what is now termed "prehabilitation", which aims to maximise postoperative recovery. This is discussed in more detail in the section below. For ERAS protocols, which most robotic centres will have in place, patients are educated and counselled regarding the procedure and recovery, medically optimized, and encouraged to change their diet preoperatively to include carbohydrate loading. Pre-operative low residue diet for 24 h with 6 h fasting for solids and 2 h for fluids is also recommended.

Surgical technique for male RARC

Applying a modular approach to the technique of male RARC has a number of advantages. It provides a methodical step by step perspective to the procedure that facilitates learning, allows smooth progress through what is a lengthy procedure, allows the operating surgeon be aware of specific steps that may have complications which can be avoided, and ultimately may reduce operating time as experience is gained^[12]. Male RARC include the steps of ureteric dissection, dissection of the anterior rectal space, dissection of the lateral rectal space, mobilization of the bladder and urethral transection, extended lymph node dissection (ELND), specimen removal, and urinary diversion. These sections will be discussed individually, before discussing specific techniques for NS (see [Figures 1-16](#)).

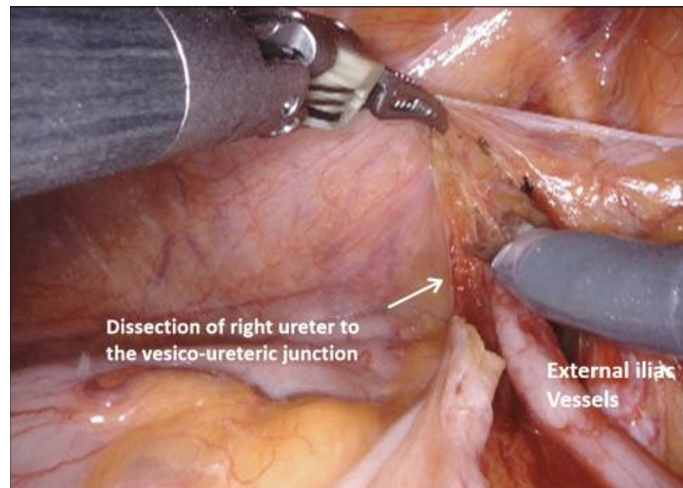


Figure 1. Right ureteric dissection.



Figure 2. Clipping of the right ureter just above the right vesico-ureteric junction.

Following informed consent, once in the operating room the patient receives a general anaesthetic and is then placed in lithotomy position with maximal Trendelenburg tilt. With arms fixed to the side of the body, a pneumatic calf compressor is attached and the upper torso covered by a warming blanket. Broad spectrum antibiotic prophylaxis is administered at induction. Per-urethral bladder catheter is placed. Thromboprophylaxis is given in recovery, and continued for 1 month postoperatively.

Trocar placement

This is similar to a robotic prostatectomy, but the trocar placement is shifted cranially. An 8 mm camera port is inserted at a left paramedian point 5-6 cm above the umbilicus, with 2 further 8 mm robotic ports placed 8-10 cm on either side, at the level of umbilicus. A further 8-10 cm lateral to the left port, a 15 mm port is inserted, 2-3 cm superomedial to the left anterior superior iliac spine (ASIS). This is later used to pass the bowel staplers and also serves as the port for the 4th arm. There are 2 other 12 mm assistant ports, one between the camera and the right robotic port and another one 2-3 cm superomedial to the right ASIS^[12].

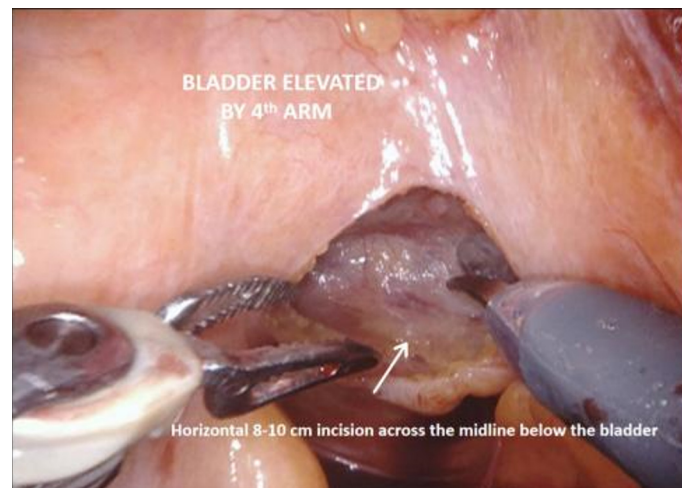


Figure 3. Posterior dissection, with horizontal incision of peritoneum just below the elevated bladder.

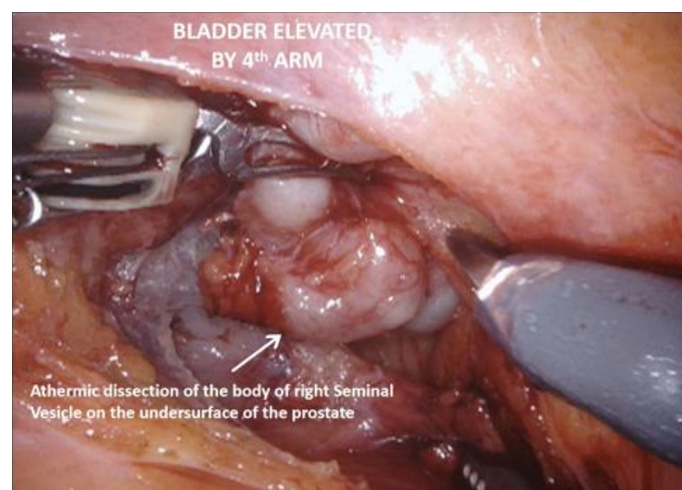


Figure 4. Posterior dissection, with athermic dissection of the body of the right seminal vesicle.

Ureteric dissection

The operation begins with dissection and division of the distal end of the ureters with clips bilaterally, generally first on the right side as the sigmoid colon may be attached to the peritoneum on this side and require adhesiolysis. The ureters can be found entering the pelvis beneath the peritoneum overlying the bifurcation of the common iliac vessels. Incising the peritoneum at this point may reveal their location, and the fourth arm is helpful in retracting the sigmoid colon on the left side. When dissecting distally towards the uretero-vesical junction, it is important to minimize handling of the ureters and leave as much tissue on them as possible to prevent compromising the blood supply and reducing the risk of ureteric strictures long term.

Anterior rectal space

The vasa are localized crossing from lateral to medial beneath the peritoneum, towards the SVs. The fourth arm is used to elevate the peritoneum and then an 8-10 cm incision is made horizontally across the midline below the bladder, extending proximally on either side towards the bifurcation of the common iliac vessels.

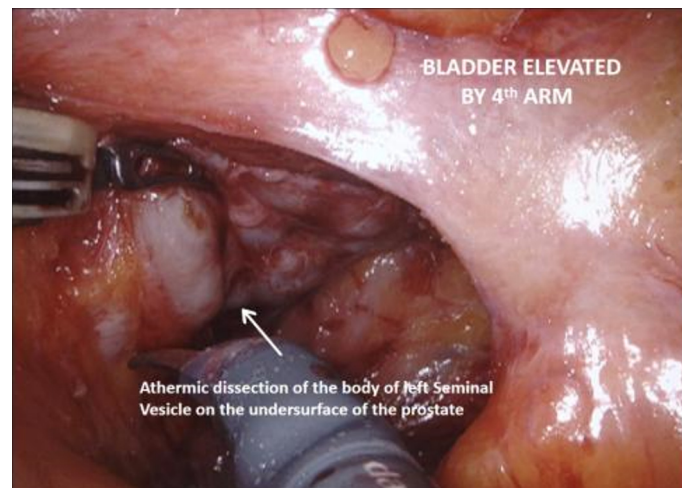


Figure 5. Posterior dissection, with athermic dissection of the body of the left seminal vesicle.

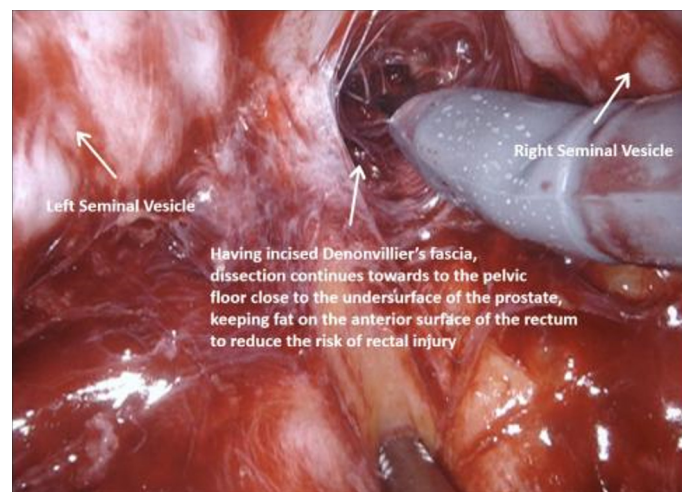


Figure 6. Post dissection, with incision of Denonvillier's fascia, and further dissection towards the pelvic floor close to the undersurface of the prostate. Fat is left on the anterior surface of the rectum to reduce the risk of rectal injury.

The vasa are then divided and the SVs dissected, avoiding cautery and using clips to divide vessels, to avoid injury to the cell bodies of the pelvic plexus. Once Denonvillier's fascia is exposed, this is divided and the plane posterior to the prostate is opened, continuing down to the pelvic floor. Preserving the fat anterior to the rectum helps to prevent rectal injury.

Lateral rectal space

Next the peritoneum lateral to the umbilical ligaments is incised, and retzius space is opened down to the pelvic floor, revealing the endopelvic fascia. The bladder is still attached by the urachus to the anterior abdominal wall and is elevated and put under traction by the fourth arm. Coming back to the lateral pedicle, the superior vesical artery is isolated, and can be divided between Hem-o-lok® clips or by LigaSure™ instrument. The anterior division of the internal iliac artery can be seen, which gives rise to the inferior vesical artery. This then divides into the urethral artery and capsular arteries, the latter of which are preserved because they contribute to the PNVB. The inferior vesical and urethral artery may be clipped or divided by LigaSure™ as above. Moving down to the pelvic floor, the lateral aspects of the prostate are

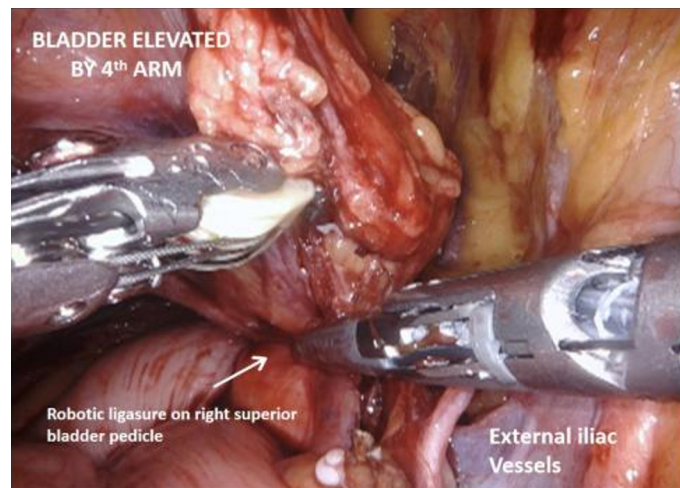


Figure 7. Ligasure of right superior bladder pedicle.

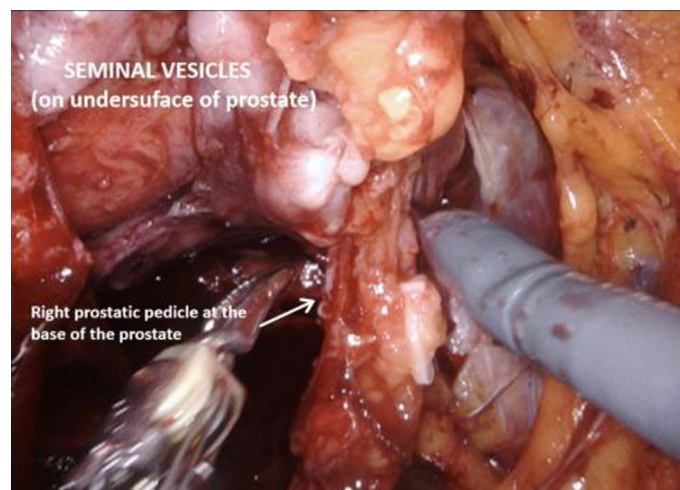


Figure 8. Ligasure of right prostatic pedicle at the base of the prostate.

mobilized and the endopelvic fascia may be opened, which frees the apex of the prostate with puboprostatic ligaments, urethra and dorsal vein complex. This is an area familiar to prostatectomists, and careful dissection in this area is crucial to functional outcomes.

Urethral transection and mobilisation of the bladder

The medial umbilical ligament and urachus are divided to free the bladder from the anterior abdominal wall, which allows easier dissection of the prostatic apex. During this part of the procedure, it is important to avoid injury to the inferior epigastric vessels. The pneumoperitoneum is increased to 20 mmHg, and the dorsal vein complex is ligated and divided, revealing the underlying urethra. If an intracorporeal neobladder is planned, urethral transection aims to preserve as much urethral length as possible, and a urethral margin specimen is sent for frozen section to rule out urethral tumour invasion. The urethra with catheter *in situ* is clipped and divided which prevent tumour spillage from the radical cystectomy specimen.

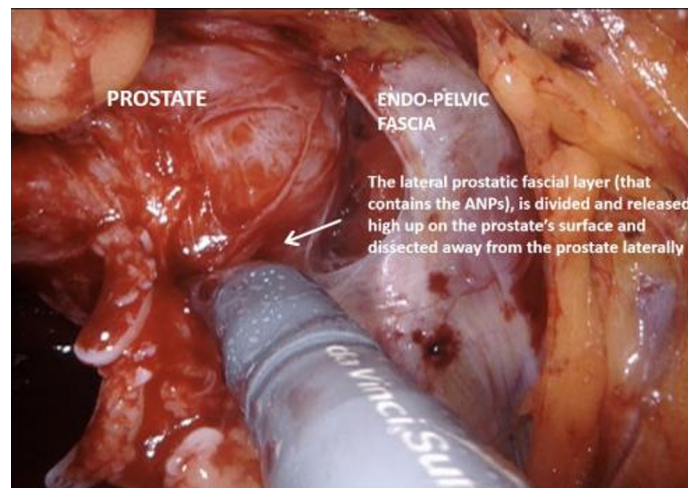


Figure 9. High release of the lateral prostatic fascia containing putative accessory nerve pathways (ANPs), with subsequent dissection of the neurovascular bundle laterally, away from the prostate.

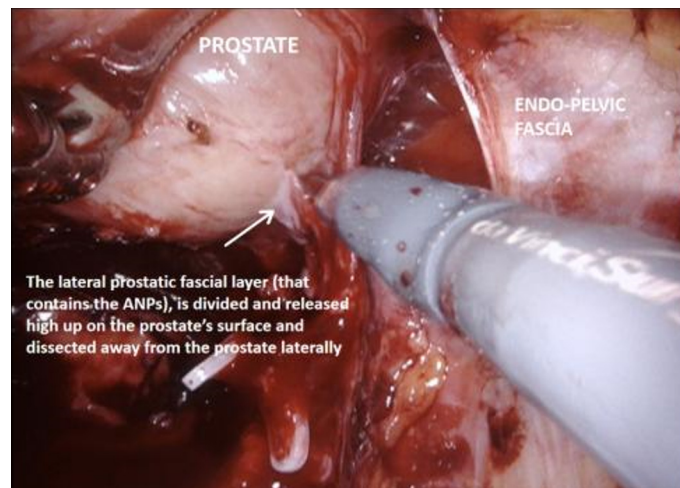


Figure 10. Further dissection of the lateral prostatic fascia and neurovascular bundle laterally, away from the prostate.

Extended lymph node dissection

This is generally performed once the cystectomy is complete so that right and left en bloc lymph node packets can be removed together with the radical cystectomy specimen. The specific technique for ELND is not discussed in this article; suffice to say sparing LNs near the vesico-ureteric junction at superior pedicle will limit injury to the hypogastric nerves carrying sympathetic fibres to the pelvic plexus^[17].

Specimen removal

The radical cystectomy specimen is placed in a large endo catch bag, with similar but smaller bags for each lymph node packet. The three bags are clipped together and can be removed through the camera port incision prior to proceeding to the urinary diversion if they are to be sent for biobanking, or alternatively can be removed through the same incision at the end of the procedure.

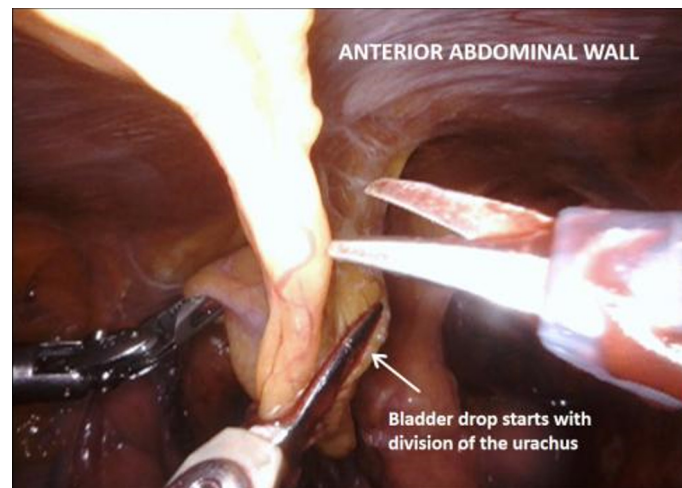


Figure 11. Bladder drop with division of the urachus.

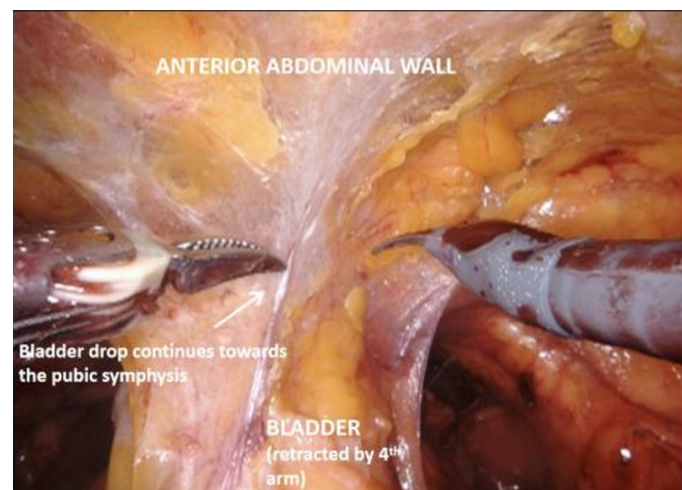


Figure 12. Bladder drop with dissection continuing down to the pubic symphysis.

Urinary diversion

The next step is the urinary diversion, which is commonly either ileal conduit or orthotopic neobladder. The neobladder is in keeping with a NS approach by aiming to maximise functional outcomes with minimal effect on body image, analogous to the pelvic organ sparing approach in women. By avoiding a urostomy bag, as well as reducing the risk of erectile dysfunction as much as possible, the combined result of male NS and neobladder will facilitate a return to sexual activity.

Nerve sparing technique

With the trizonal neuroanatomy described above in mind^[11], the NS technique begins once the SVs dissection starts. Avoidance of cautery and clipping small vessels for hemostasis prevents injury to the cell bodies in the PNP, especially around the middle and the tips of the SVs. As the dissection continues forward, vessels may be clipped as close as possible to the prostate, again avoiding cautery with athermal dissection. Once at the base of the prostate, the lateral fascial layer that contains the ANPs, is divided and released high up on the prostate's surface and dissected away from the prostate laterally, to prevent injury to

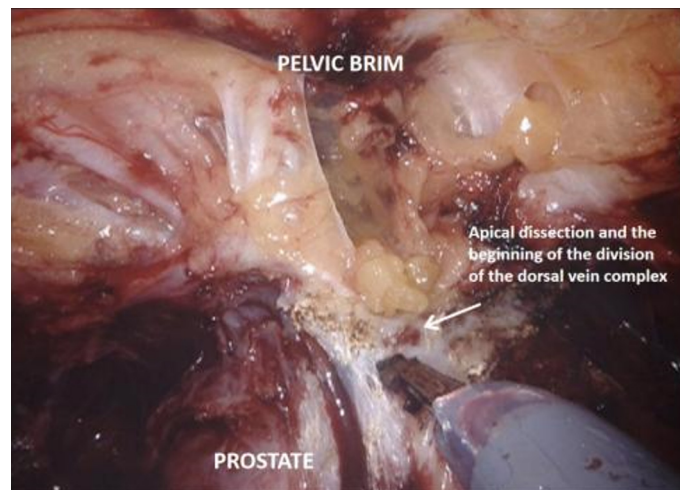


Figure 13. Dissection of the prostatic apex before division of the dorsal vein complex.

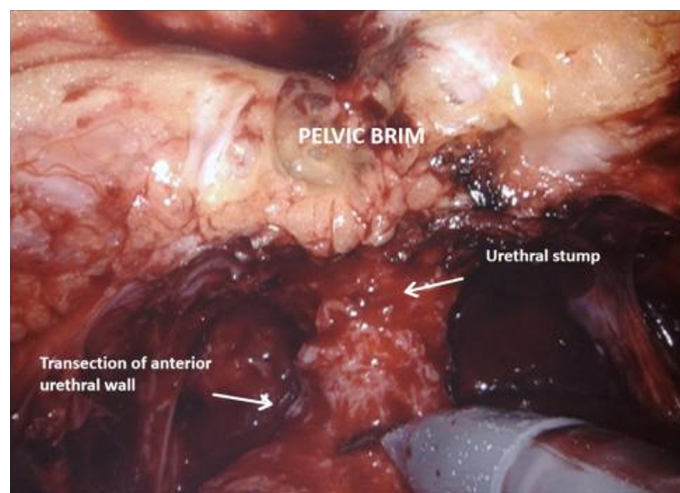


Figure 14. Transection of the anterior urethral wall.

the ANPs. Further inferiorly the PNVB may be seen and is also dissected away from the prostate laterally, with as little tension and cautery as possible. Once this plane is found, dissection continues towards the prostatic apex, with the lateral prostatic fascia and PNVB laterally, down to the pelvic floor, until the prostate-urethral junction. At the apex, the PNVBs run alongside the urethra at 10 and 2 o'clock, and careful suturing of the dorsal vein should avoid these areas, as well as making sure to minimize dissection around the surrounding structures and muscle tissue to prevent injuring branches of the pudendal nerves and accessory vessels^[17]. A continuing awareness for nerve preservation is important during the ELND, where sparing lymph nodes at the lateral pedicle between the ureters and bladder near the vesico-ureteric junction prevents injury to the hypogastric nerves carrying sympathetic fibres to the pelvic plexus (described above)^[17].

Technical variations on NS

Two variations on the common NS approach have also been described including capsule sparing cystectomy and SV sparing cysto-prostatectomy^[15]. The capsule sparing technique involves a pre cystectomy

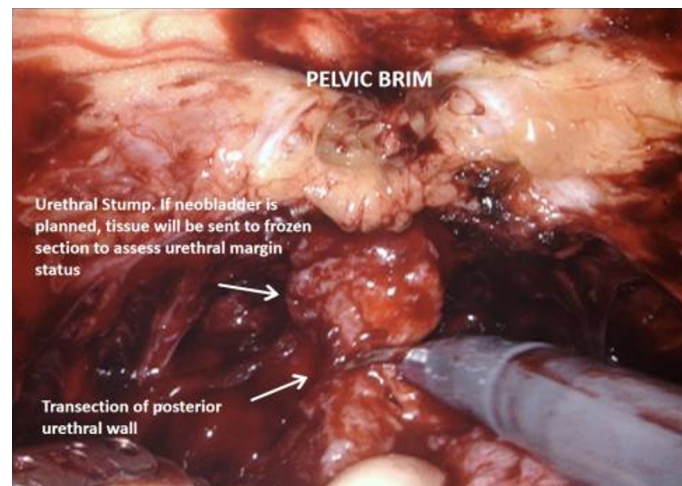


Figure 15. Transection of the posterior urethral wall.



Figure 16. Cysto-prostatectomy specimen.

transurethral resection of prostate and prostate biopsies to rule out prostate cancer, followed by RARC with preservation of prostate capsule, vasa and SVs with the trizonal pelvic plexus remaining intact^[15,18]. In a prospective randomised controlled trial, no significant difference in functional outcomes was seen between this approach and the commoner NS approach above^[19]. For the SV sparing technique, the prostatectomy part of the cysto-prostatectomy is down by retrograde intrafascial dissection sparing the vasa, SVs and once again, the trizonal architecture of the pelvic plexus. This technique was undertaken by some of the series presented in [Table 1](#), with satisfactory outcomes^[18,20], but more study is required to determine whether this technique is superior to the more standard approach.

RESULTS (SEE [Appendix 1](#), [Tables 1 AND 2](#))

An EMBASE database search was done with key words of robotic, cystectomy, male and nerve sparing, which included journal articles, abstract publications or conference abstracts, available in English or translated to English. Previous review articles were also checked as sources of original work not otherwise found on initial search. Duplications and publications with no description of post-operative functional

Table 1. Functional outcomes

Ref.	Year	Type of study	No. of male patients	Nerve sparing	Continence	Sexual function	Duration of follow-up (months)
Balbay <i>et al.</i> ^[21]	2020	Case series	18	77.78%	DT - 76.92% NT - 53.85%	Baseline decrease by 15 points	47.3
Gok <i>et al.</i> ^[22]	2019	Retrospective analysis	92	90.8%	DT - 65% NT - 42%	Baseline decrease by 24 points	27.1
Liu <i>et al.</i> ^[23]	2019	Case series	12	100%	ND	S = 41.7% I = 25% N = 33.3%	12
Zarranz <i>et al.</i> ^[24]	2019	Case series - CA	46	67.39%	ND	S = 91% of NS	24
Kwon <i>et al.</i> ^[25]	2018	Retrospective cohort - CA	40	37.5%	ND	40%	12
Palou <i>et al.</i> ^[39]	2017	Case report - CA	1	100%	100%	IIEF 17	7
Asimakopoulos <i>et al.</i> ^[17]	2016	Case series	40	100%	DT - 75% NT - 72.5%	77.5%	26.5
Nyame <i>et al.</i> ^[26]	2016	Case series	3	100%	100%	100%	28.2
Colombo <i>et al.</i> ^[18]	2015	Retrospective analysis	90	100%	DT - 88.8% NT - 84.4%	65%	58
Jacobs <i>et al.</i> ^[19]	2015	Randomised controlled trial	40	100%	Baseline decrease by 20 ± 31 points	Baseline decrease by 12 ± 20 points	38
Schwentner <i>et al.</i> ^[29]	2015	Retrospective analysis	50	92%	DT - 88% NT - 55.1% overall	54% overall	30.3
Haberman <i>et al.</i> ^[27]	2014	Retrospective analysis	254	11.42%	ND	S - 45% I - 21% N - 34%	32.9
Menon <i>et al.</i> ^[28]	2003	Case series - CA	2	100%	ND	I = 100% IIEF score of 9&10	2.8
Krishnan <i>et al.</i> ^[30]	2014	Case series	3	100%	100%	100%	ND
Tyritzis <i>et al.</i> ^[38]	2013	Retrospective analysis	62	66.13%	DT - 88.2% NT - 73.5%	84.37%	12
Rey <i>et al.</i> ^[31]	2013	Case report - CA	1	100%	100%	100%	24
Boc <i>et al.</i> ^[32]	2013	Case series - CA	2	100%	ND	100%	6
Canda <i>et al.</i> ^[40]	2012	Case series	25	92%	DT - 73.3% NT - 46.7%	ND	6.3
Jonsson <i>et al.</i> ^[33]	2011	Prospective nonrandomised	36	55%	DT - 83% NT - 66%	75%	25
Akbulut <i>et al.</i> ^[34]	2011	Case series	12	91.67%	DT - 54.5% NT - ND	9%	7.1
Ong <i>et al.</i> ^[20]	2010	Case series	31	100%	DT - 93% NT - 66%	79%	18
Palou <i>et al.</i> ^[35]	2010	Case series	12	100%	DT - 90.9% NT - 72.72%	90.9%	16.5
Murphy <i>et al.</i> ^[36]	2008	Case series	23	20%	DT - 100% NT - 75%	75%	17
Mottrie <i>et al.</i> ^[37]	2007	Case series	27	25.9%	86%	86%	10.2
Kessler <i>et al.</i> ^[13]	2004	Retrospective analysis	331	77.34%	DT - 96% NT - 88%	35.93%	24

CA: Conference abstract; ND: not described; DT: day time; NT: night time; S: satisfactory; I: insufficient; N: no erection; NS: nerve sparing.

outcome were excluded. When there was no mention about any sparing of the neurovascular bundles (NVBs), the procedure was taken a non-nerve-sparing procedure and thus also excluded along with the procedures performed without robotic assistance. A total number of 25 relevant publications were selected investigating male NS RARC, assessing functional outcomes with respect to potency and urinary continence along with other surgical standard indicators.

Table 2. Perioperative and oncological outcomes

Ref.	Year	No. of male patients	Complications	Positive surgical margins	Survival rates	Duration of follow-up (months)
Balbaj et al. ^[21]	2020	18	Early - 9% (\geq Gr3) Late - 18% (\geq Gr3)	13.6%	CSS, OS & RFS at 2 years - 68.6%, 66.0% & 69.7%	47.3
Gok et al. ^[22]	2019	92	Early - 20.4% (\geq Gr3) Late - 7.1% (\geq Gr3)	2%	OS & CSS at 25 months - 20.4% & 13.3%	27.1
Liu et al. ^[23]	2019	12	None	Nil	ND	12
Zarranz et al. ^[24]	2019	46	Transfusion 35%	Nil	PFS at 2 years 71%	24
Kwon et al. ^[25]	2018	40	ND	ND	OS & CSS at 5 years 86.7%	12
Palou et al. ^[39]	2017	1	Ileus - 2 days	ND	100%	7
Asimakopoulos et al. ^[17]	2016	40	Early - 30%, 2.5% (\geq Gr3) Late - 32.5%, 5% (\geq Gr3)	2.5%	1 death at 23 months	26.5
Nyame et al. ^[26]	2016	3	2 (66%) Gr2	Nil	100%	28.2
Colombo et al. ^[18]	2015	90	ND	ND	CSS - 92.2%	58
Jacobs et al. ^[19]	2015	40	47.5% (\geq Gr3)	5%	ND	38
Schwentner et al. ^[29]	2015	50	25.8% (\geq Gr3)	6.4%	CSS - 84% OS - 71%	30.3
Menon et al. ^[28]	2003	2	100% Gr1	ND	ND	2.8
Krishnan et al. ^[30]	2014	3	ND	Nil	100%	ND
Tyritzis et al. ^[38]	2013	62	At 90 days 58.5% overall 37.1% (\geq Gr3)	1.4%	OS & CSS at 2 years - 88.9%	12
Rey et al. ^[31]	2013	1	None	Nil	100%	24
Boc et al. ^[32]	2013	2	ND	Nil	100%	6
Canda et al. ^[40]	2012	25	Early - 16% (\geq Gr3) Late - 12% (\geq Gr3)	Nil	CSS - 82.6%, OS - 78.26%	6.3
Jonsson et al. ^[33]	2011	36	Early - 40% Late - 33%	2.78%	3 years CSS - 86%	25
Akbulut et al. ^[34]	2011	12	16.6% (\geq Gr3)	Nil	CSS - 72.72% OS - 63.63%	7.1
Ong et al. ^[20]	2010	31	ND	3.23%	CSS - 96.77%, OS - 93.55%	18
Palou et al. ^[35]	2010	12	ND	ND	CSS - 91.67%	16.5
Murphy et al. ^[36]	2008	23	26% overall	Nil	1 metastatic death	17

ND: Not described; PFS: progression free survival; OS: overall survival; CSS: cancer specific survival.

DISCUSSION

Different approaches have been outlined for male NS RARC^[15] and this review details the perioperative, oncological and functional outcomes (see [Tables 1](#) and [2](#)). Most series contain small numbers of patients with largely retrospective data with the associated bias of selection. Mean follow up of 27.06 months (range 2.8-58 months) was noted over all in this review. Because of the heterogeneity of study design, technique, definitions and measurements of continence and erectile function and surgeons and centres a meaningful systematic analysis of functional outcomes is challenging.

Though there are differences in defining satisfactory erectile function most encompassing definition derived from all the studies for the purposes of this review was taken as erectile function enough for penetrative sex with or without PDE5i usage. In this review, 54.32% (range 9%-100%) of patients recovered satisfactory erectile function in their post-operative follow up^[13,17-38]. This is superior to the 12%-23.8% satisfactory erectile function noted on patients who underwent a non-NS radical cystectomy^[22,30].

Continence figures are relevant to those patients undergoing orthotopic neobladder at the same time as male NS RARC and satisfactory continence is defined in the studies to be dry enough to maintain with a maximum of one pad per day. In this review, 85.06% day time continence rate (range 54.5%-100%) and 72.48% night time continence rate (range 46.7%-88%) were noted overall in patients whose NVBs were preserved^[13,17,18,20-22,26,29-31,33-40]. This is in contrast to the results of some studies, for example, Tyritzis *et al.*^[38], who noted no significant difference in continence rates between their NS and non-NS groups of patients with 88.2% and 88.9% respectively for day time continence rates at 12 months.

With the legitimate concerns for NS being the potential for clinical understaging and incomplete tumour excision, it is of note that overall surgical margin negativity was 98.2% in our review, equivalent to 1.8% positive surgical margins (PSM) (range 0%-6.4%). This compares favourably to other series performing non-NS minimally invasive radical cystectomy achieving 2.2% PSM^[41] and an overall 6% found from the results of the International Robotic Cystectomy Consortium^[42]. Much of this will be explained by patient selection which rules out pT3-4 tumours, accounting for a significant proportion of PSM cases in other studies.

Examining some of the studies reviewed in more detail, Nyame *et al.*^[26], had a very select patient group of < 40 years old men and performed bilateral nerve and apex sparing radical cystectomy who showed excellent outcomes both oncologically with 0% PSM and 66.7% recurrence free survival and functionally with all their patients being potent and continent after 28.3 months follow up. However, the demographics show that bladder cancer affects much older patients, and once again patient selection is critical. Many patients in their late 60s, early 70s may not regard potency as a priority, but this is not always the case, and although patients below the age of 65 years have better outcomes postoperatively with respect to erectile function, older patients should at least be offered the opportunity to maximise their quality of life after treatment^[13]. Canda *et al.*^[40], investigated 27 patients who underwent RARC with Studer Neobladder and found that such procedures, although technically challenging, have good surgical and pathological outcomes and satisfactory morbidity and functional results. They did caution, however, that further studies with more patients and longer follow-ups are necessary^[40]. Tyritzis *et al.*^[38], mentioned above, studied functional and oncological outcomes of patients (both male and female) that underwent RARC with totally intracorporeal neobladder. A large proportion of their cohort (41/70; 58.6%) was treated with NS procedures. Sexual function and day time continence at 12-month was satisfactory at between 70% and 90%. They supported the findings of Canda *et al.*^[40], that the complications and both functional and oncological outcomes were comparable to open radical cystectomy, demonstrating that RARC with Robotic neobladder and NS approach is a feasible and safe alternative^[38]. Haberman *et al.*^[27], evaluated the effects on post-operative erectile function of a bilateral cavernosal nerve-sparing approach to RARC in a preoperatively potent population. Their retrospective study reviewed data from 254 patients from 2003 to 2012 who had RARC. 29 out of 33 men under the age of 65 years had bilateral nerve-sparing procedure. Postoperatively, 45% of them were able to maintain satisfactory erections for penetrative intercourse with or without use of Viagra type medication. A further 21% recovered erectile function using intracavernosal injections (ICI), while 34% were unable to use ICI or decided recovering their potency was no longer an issue. They further observed no significant difference between those who recovered potency and those who did not based on a number of parameters, including comorbidities, operating time, tumour stage and age of patient. Despite NS, there was no PSMs and no local cancer recurrence. Based on these results, they concluded that NS RARC improved postoperative erectile function without having to compromise oncologic outcomes^[27]. Colombo *et al.*^[18], also showed good outcomes in their patient cohort but acknowledged patients were highly selected comprising only 8.8% of all the patients who had a radical cystectomy during the study period. A similar patient cohort demographic was noted by Haberman *et al.*^[27], with only 11.4% of their patients having a NS operation and

14.2% by Ong *et al.*^[20]. Interestingly addressing the issue of potential PSM from incidental prostate cancer in patients undergoing male NS RARC, Chessa *et al.*^[43], reported no difference in prostate cancer PSM rates.

Prehabilitation, rehabilitation, adjunctive strategies and lifestyle changes

ERAS protocols have been gaining in popularity and are now utilized by most robotic urology centres. Surgeons have recognized the importance of preparing patients for a major operation such as an RARC with a multimodal approach, becoming increasingly part of “prehabilitation” programs, aiming to institute lifestyle changes and improve physical fitness before surgery is undertaken. Preoperative smoking cessation has shown to positively impact post-operative outcomes^[44], and, for example, Minella applied prehabilitation tactics in a randomised controlled study group with exercise, nutritional advice and anxiety reducing interventions, finding that patients who went through the program did better than the control group at their 4-week post-operative functional capacity evaluation^[45]. Although some of the evidence is conflicting, penile and pelvic floor rehabilitation has been described as part of post-operative follow up for any radical pelvic surgery not only to improve potency but also urinary continence and bowel function postoperatively^[46]. In fact, the field of bladder cancer surgery may learn from prostatectomists who employ a number of pre-, intra- and post-operative strategies to improve functional outcomes with both urinary continence and erectile function.

With respect to erectile function, maximizing post-operative recovery begins with pre-operative work up when the patient’s erectile function is assessed objectively. Modalities may include a thorough clinical assessment to stage the disease, IIEF-6 questionnaire, psychosocial assessment including partner factors^[47], sleep assessment^[48] and, if necessary, penile doppler ultrasound^[49]. Similarly, starting pelvic floor exercises with pelvic floor muscle training (PFMT) before the procedure may benefit post-operative continence in patients undergoing orthotopic neobladder^[50]. Intra-operative strategies stress the importance of the accessory pudendal arteries preservation for erectile function^[51], as well as other techniques such as the application of dehydrated human amniotic membrane which has been proposed to accelerate nerve regeneration^[52]. Postoperatively a multiple modal approach is advocated for rehabilitation of both erectile and urinary function. Ongoing PFMT as well as biofeedback have been used to improve continence^[50]. For penile rehabilitation, strategies include phosphodiesterase-5 inhibitors, intracavernosal injection therapy, vacuum erection devices, MUSE Alprostadil urethral suppository, pelvic floor therapy, penile vibrostimulation, hormonal factor correction, penile implant, hyperbaric oxygen therapy, extracorporeal shockwave therapy, psychosocial therapies and nerve grafting techniques^[53].

Clearly not all of these strategies will apply to bladder cancer patients undergoing male NS RARC with or without neobladder, but by inference, patients will likely have less comorbidities, and be highly motivated to gain as much quality of life functionally after their procedure as possible. The success of these strategies for patients undergoing prostate cancer surgery would suggest these adjunctive treatments are worthy of further investigation for the field of bladder cancer surgery.

In conclusion, male NS RARC for appropriately selected patients, in experienced hands will offer good functional outcomes leading to a better quality of life for those patients who benefit. Results from the series reviewed suggest the technique is both feasible and safe, without compromising longer term oncological results. With the more widespread use of ERAS protocols, and the introduction of prehabilitation and lifestyle programs, patients will also be able to contribute more proactively to their functional recovery, and help with the technical success of the operation. In addition to basic surgical expertise, there are a number of adjunctive strategies aiming to improve urinary and erectile function, and the results demonstrated for

prostate cancer surgery suggests their use in the field of bladder cancer surgery may warrant further investigation.

DECLARATIONS

Authors' contributions

Performed data analysis, interpretation and manuscript write up: Thinagaran JKR

Technical description of operative steps, data acquisition: Dovey Z

Review of manuscript: Maqboul F

Review and substantial contributions to conception and design of study: Dovey Z, Wiklund P

Availability of data and materials

Tables 1 and 2 provide details of the systematic review. Appendix A PRISMA METHODOLOGY. Figures to illustrate NS technique.

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Conflicts of interest

Dr. Dovey Z is Medical Director and stock owner (with certificate of shares) of Medtech Holdings Ltd.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Review

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An investigative review on the current role and outcomes of salvage radical cystectomy

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Abstract

Salvage radical cystectomy (SRC) is currently performed after failure of a trimodal treatment (TMT) for muscle invasive bladder cancer (MIBC) and also as a palliative surgery to manage bladder cancer-related symptoms. We reviewed the available literature to assess the current outcomes of SRC. A comprehensive research of the Medline and Embase databases was carried out by following the Preferred Items for Systematic Reviews and Meta-Analysis. Bladder cancer, radiotherapy, salvage, and cystectomy were the main keywords used in the research. Due to the lack of studies, no time restriction was applied, however only English language and only studies using Clavien-Dindo Grade (CCS) to report complications were considered. Overall, 285 studies were identified, of which 41 studies were considered eligible for the purpose of this review. No comparative studies were found between TMT plus SRC and immediate radical cystectomy. Thirteen studies reported oncological outcomes after TMT. The five-year mean disease free survival rate of patients who underwent SRC after TMT was reported to be about 50% and the 5-year OS rate was between 33% and 48%. Three studies including fewer than 20 patients performed SRC with palliative purpose. Although no perioperative death occurred, patients were highly selected. Overall, 4 studies graded surgery-related complications by CCS. The rate of major complications, defined as CCS ≥ 3 , was reported to be between 16% and 32%, most of them being gastrointestinal complications. SRC still preserves a role in the management of MIBC, being part of TMT and palliative care in highly selected patients. However, this surgery is at higher risk of complications and is associated with incontinent urinary diversion, thus an accurate discussion during patient counseling is advisable.



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Keywords: Salvage radical cystectomy, bladder cancer, radiotherapy, hematuria

INTRODUCTION

Nowadays, the improvements in medical, surgical, and anesthetic techniques have dramatically reduced the morbidity and mortality associated with radical cystectomy (RC), but it is still considered a major surgery with a 0.7%-42% risk of developing high-grade complications (defined as Clavien-Dindo Grade ≥ 3) and 0.4%-7% mortality rate^[1].

RC is the standard treatment for muscle invasive bladder cancer (MIBC) recommended for T2-4a, No-NxMo MIBC, in the case of T1 bladder cancer not responsive to BCG treatment or not controllable by TURB^[2]. In addition to the surgical skill required to perform RC, one of the challenges regarding this surgery is related to the patient's medical condition. Surgery is generally performed in frail elderly patients, with several comorbidities, intractable gross hematuria and anemia, and some of them (about 10%-15%) are metastatic^[2].

The term "salvage radical cystectomy" (SRC) initially referred to RC performed after bladder radiotherapy and implied an unfavorable meaning for the more elevated skill required to accomplish the procedure as well as its higher morbidity and mortality rate. Nowadays, SRC term is largely used when the bladder is removed in patients affected of MIBC who previously underwent unsuccessful initial trimodal treatment (TMT) or when RC is carried out for a purely palliative purpose aimed at treating only fatal disease-related complications and symptoms without a true oncologic intent.

We performed a literature review with the aim of summarizing the current role of salvage radical cystectomy in those two clinical settings of MIBC, after a failed initial treatment or as a palliative surgery.

METHODS

In January 2021, a literature research on PubMed/Medline, Scopus, and Google Scholar databases was performed by using the following keywords: bladder cancer, muscle invasive bladder cancer, bladder preservation, radiotherapy, pelvic irradiation, and salvage cystectomy. The title and the abstract of the retrieved studies were assessed for their relevance and, subsequently, their reference lists were screened to identify further studies. No time limit was applied to the research strategy, however English language restriction was used and no abstracts were included. In particular, two authors (Cicione A and Lombardo R) selected studies which included patients affected by MIBC who underwent salvage cystectomy as a subsequent treatment for supplementary control of disease and studies where RC was carried out only for a symptom-control purpose. Moreover, only studies using the Clavien-Dindo Classification System^[3] were used to assess surgery complications of SRC.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were respected in the preparation of this scoping review^[4] [Figure 1].

RESULTS

Salvage radical cystectomy after trimodal therapy: oncological outcomes

Most of the retrieved studies reporting survival rates after SRC referred to cystectomy performed after preserving bladder treatment for MIBC [Table 1]^[5-18]. Moreover, there are no completed randomized trials comparing the oncological outcomes of preserving bladder treatment with RC^[2], whereby the current oncological benefit of SRC after a bladder preserving treatment is based mainly on surgical series. At

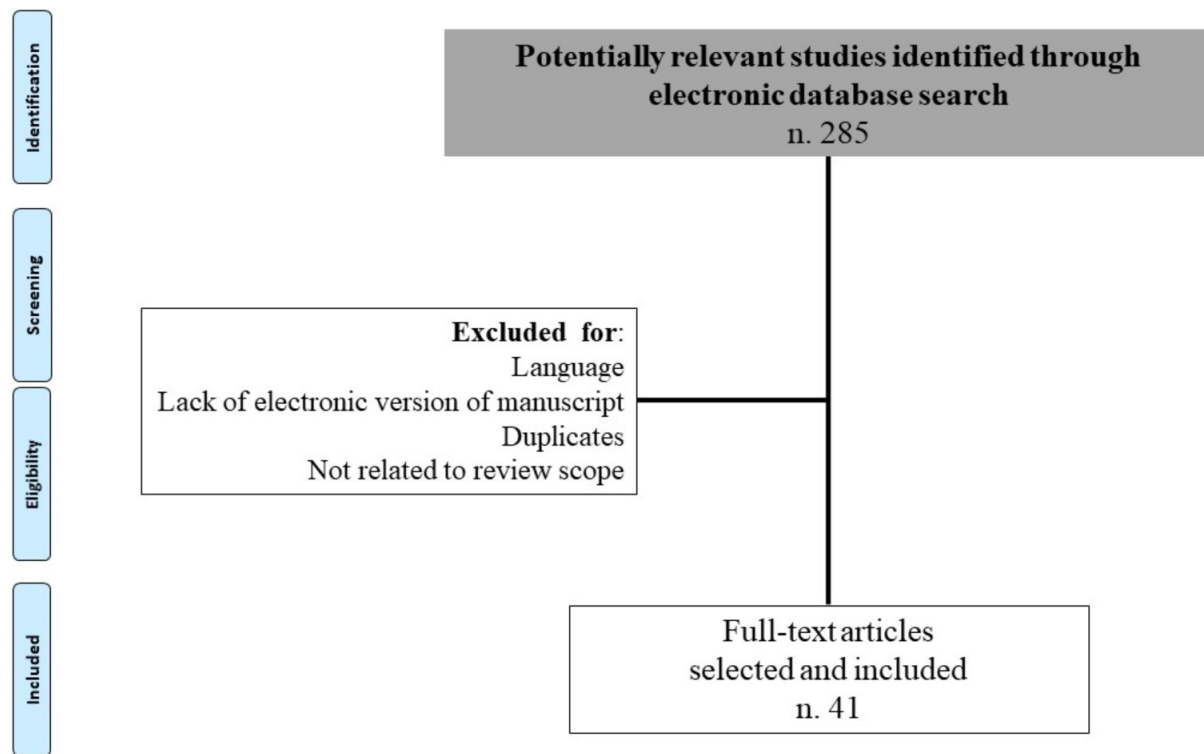


Figure 1. Flow diagram of the literature research.

present, preserving bladder treatment is proposed to patients who refuse or are unfit for RC. The current clinical guidelines of the most popular oncological and urological societies [Table 2] suggest a bladder-preserving treatment known as “trimodality” or “trimodal treatment” to highly selected patients. The ideal patient is affected by an early stage MIBC without limpho-vascular invasion or distant metastases, in the absence of multifocal carcinoma *in situ* and hydronephrosis with a good bladder function and compliance for a long and close follow-up. The TMT protocol consists of preliminary extensive TURB aimed to remove all the visible tumor and allow a maximal focused radiation on the smallest tumor volume. Rödel *et al.*^[19] showed that the extensiveness of TURB is the key component for any successful bladder-preservation strategy, and it was the only independent prognostic factor for long-term survival in their MIBCs series. Furthermore, the optimal radiation technique and dose have not yet been standardized, but two main protocols are used: split and continuous^[20]. The first one includes bladder radiation with at least 40-45 Gy to the pelvis and concurrent radiosensitizing chemotherapy followed by an additional radiation boost to the bladder (20-25 Gy) if a complete response is documented on repeat biopsy^[21]. The latter consists of full dose RT (64-66 Gy) with concurrent chemotherapy after maximal TURB^[19]. Despite the controversies on the optimal RT protocols, the inferiority of RT alone compared to RT plus chemotherapy has been well established^[2]. Thus, SRC in TMT setting is reserved for those patients who do not respond to treatment (immediate cystectomy) or develop an invasive recurrence during follow-up (delayed cystectomy).

The first report on SRC was published in 1964 and reported discouraging results with three out of four patients dying due to sepsis. However, further series have been published over the years [Table 1]. One of the largest series included 159 patients initially affected by T2-T4 NxM0 MIBC that was managed by TMT^[11]. All patients had a good performance status (EGOG score of 0-3) and cisplatin-based chemotherapy was administered. Over a mean follow-up of 11 years, 24% of patients required SRC after 12 months from initial treatment. After SRC, the median overall survival (OS) was 15 months. No significative difference in

Table 1. Studies reporting survival outcomes after SRC following trimodal treatment for MIBC

Ref.	Median age	Follow up	SRC patients (n)	Oncological outcomes
Eswara <i>et al.</i> ^[5]	69.4 (27.5-88.9)	12 years	102	Disease-free survival rates in the immediate and delayed groups was 38% and 61%, respectively, at 10 years ($P < 0.05$) with an overall 10-year disease-free survival rate of 48% for the entire cohort
George <i>et al.</i> ^[6]	-	48.5 months	11	7 patients died of disease, 2 died of other cause at 27 and 53 months, 1 was alive with distant metastases, and 1 was alive with no evidence of disease
Cooke <i>et al.</i> ^[11]	65 (41-75)	11 years	38	The median time to cystectomy after the primary treatment was 12 months (range 56 days to 10 years). The median survival after cystectomy was 15 months (95%CI: 9-23 months)
Nieuwenhuijzen <i>et al.</i> ^[12]	-	-	27	The 3- and 5-year survival probability after cystectomy was 46% (95%CI: 26-65) and 33% (11-54)
Bochner <i>et al.</i> ^[13]	-	-	13	After a median follow up of 28 months, 15 patients (82%) were without evidence of disease
Crawford <i>et al.</i> ^[14]	-	-	34	About 50% of patients died for disease progression with a mean survival time of 14.5 months
Freiha <i>et al.</i> ^[15]	-	-	40	45% patients alive after 5 years
Swanson <i>et al.</i> ^[16]	63 (41-79)	-	62	14.5 months was the median time from the initial diagnosis of bladder cancer to cystectomy 5-year survival rate after cystectomy for the whole group was 43.2%
Abratt <i>et al.</i> ^[17]	62 (36-82)	-	46	SRC was need after a mean of 11 months after radiotherapy. The overall 5-year survival rate was 43% while it was worse (7%) in case of higher grade and stage
Nurmi <i>et al.</i> ^[18]	61 (32-74)	-	20	Intractable voiding symptoms were also reason for SRC. The overall 5-year survival rate after the operation was 61%
Linell <i>et al.</i> ^[7]	66 (52-75)	-	19	SRC performed both for tumour recurrence and/or bladder symptoms The 5-year survival rate was 5 %
Konnak <i>et al.</i> ^[8]	65 (50-82)	-	18	Interval between RT and SRC ranged between 6 months-12 years, mean 2.5 years The overall crude 5-year survival from the time of cystectomy was 50%
Smith <i>et al.</i> ^[9]	-	-	80	The over-all 5-year survival rate was 37% while the postoperative hospital mortality rate was 5%
Kulkarni <i>et al.</i> ^[10]	71 (37-95)	4.51 years	6	No significant difference in terms of 5-years DFS between radical cystectomy and TMT (respectively, 73.2% vs. 76.6%) was computed. SRC was performed in 6 (10.7%) of 56 patients who received TMT

SRC: Salvage radical cystectomy; MIBC: muscle invasive bladder cancer; DFS: disease free survival; TMT: trimodal treatment.

terms of survival was found for patients receiving SRC or not^[11].

Eswara *et al.*^[5] retrospectively analyzed clinical data of 348 patients undergoing TMT with extensive TURB, cisplatin-based chemotherapy, and almost 40 Gy radiotherapy. Patient's features were similar to a previous study by Cooke *et al.*^[11] except for the presence of hydronephrosis that was considered an exclusion criterion for trimodal treatment. On average, SRC was carried out no more than 10.3 months after the last dose of chemotherapy. The 10-year disease free survival rate (DFS) from SRC was 48%, which significantly improved (up to 61%) when the surgery was delayed compared to conservative treatment.

Interestingly, Schuetthfort *et al.*^[22] recently used a pooled analysis method to assess the efficacy of trimodal treatment. They reviewed the available literature and identified 73 studies including 9110 patients. The analysis showed that SRC was necessary in 19.2% of cases and 5- and 10-year DFS rates were, respectively, 54.3% (95%CI: 48.6-60.1) and 45.6% (95%CI: 41.6-49.6).

Table 2. Current guidelines on bladder preserving approaches for MIBC

Association	Patient selection criteria	Radiotherapy	Chemotherapy
AUA	Highly selected patient - Unfit for RC - Tumor resectable by TURB (< 3cm) - Absence of multifocal CIS and hydronephrosis and T3/T4 tumors - No histology variants - Well informed patient (40% subsequent RC) - Adequate bladder function - Follow-up	Halt the radiation at a dose of 40-45 Gy (approximately 2/3 of the total dose), repeat a cystoscopy with re-biopsy, and, if muscle invasive tumor still persists, recommend cystectomy at that time	Many prospective studies have reported high rates of local control (> 70%) in patients selected for treatment on protocols that included cisplatin with or without 5-FU
ESMO	Option for patients seeking an alternative to cystectomy and a palliative option for those who are medically unfit for surgery Ideal patient: early tumour stage (including high-risk T1 disease T2 < 5 cm), a visibly complete TURBT, absence of associated CIS and ureteral obstruction and adequate bladder capacity and function Lifelong surveillance is required to achieve optimal results	In case of bladder preservation with radiotherapy, combination with a radiosensitizer is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine	
EAU	Reasonable treatment option in well-selected patients as well as patients with a contraindication for surgery High level of patient compliance is need, absence of carcinoma <i>in situ</i> , absence or presence of hydronephrosis, optimal debulking of initial cancer	A standard radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40 Gy, with a boost to the whole bladder of 54 Gy and a further tumour boost, with a total dose of 64 Gy	Different chemotherapy regimens have been used, but most evidence exists for cisplatin and mitomycin C plus 5-FU. In addition to these agents, other schedules have also been used, such as hypoxic cell sensitisation with nicotinamide, carbogen and gemcitabine, without clear preference for a specific radiosensitizer

AUA: American Urological Association; ESMO: European Society for Medical Oncology; EAU: European Association of Urology; MIBC: muscle invasive bladder cancer; RC: radical cystectomy.

Thus, 10%-30% of patients will require SRC after initial curative TMT with a mean 5-year DFS of 50% and 5-year OS rate of 33%-48%. However, those findings may be biased, hypothesizing that all patients requiring SRC were fit for surgery and studies included only patients with \geq T2 N0M0 bladder cancer. In patients undergoing RC at primary MIBC diagnosis, Stein *et al.*^[23] showed an OS at 5 and 10 years of 78% and 56%, respectively, in the presence of organ confined disease with no lymph node involvement. Those rates were dramatically reduced in the presence of extravesical disease extension (5-year OS = 55%; 10-year OS = 27%) and lymph nodes involvement (5-year OS = 31%; 10-year OS = 23%).

However, the rate of disease-free survival after SRC is higher than in the absence of treatment. Martini *et al.*^[24] evaluated the natural history of MIBC in the absence of treatment by analyzing 64 patients > 79 years old affected by T2-T4 N0 high-grade bladder cancer who did not receive any treatment. They found a

5-year OS of 5% (95%CI: 1%-12%). Furthermore, the median time to death from any cause was 9 months. As predictable, on multivariable analyses, after adjusting for age at diagnosis, sex, clinical stage, and tumor stage, untreated patients had a higher risk of death from any cause [hazard ratio (HR) = 2.63; 95%CI: 1.65-4.19; $P < 0.001$], progression to distant metastasis (HR = 2.40; 95%CI: 1.28-4.51; $P = 0.006$), and cancer specific mortality (HR = 2.02; 95%CI: 1.24-3.30; $P = 0.005$).

Overall, between 10% and 15% of patients are already metastatic at diagnosis with a median survival rarely exceeding 3-6 months before the development of effective chemotherapy^[2]. Mak *et al.*^[21] reported the rate of metastatic disease among 468 patients treated with TMT, which ranged from 32% to 35%. However, no studies on SRC with curative intent in this stage of disease were retrieved except for a palliative purpose.

Thus, we found that up to 30% of patients treated with primary TMT with a curative intent subsequently required SRC after 1 year of TMT. Although no comparative studies with RC are still available, SRC with a curative intent seems to be feasible with acceptable oncological outcomes. Moreover, the recent introduction of immunotherapy in the chemotherapeutic armamentarium encourages further assessing approaches that preserve the bladder.

Salvage radical cystectomy as palliative care: surgical outcomes

Bladder cancer is related to a significant morbidity for its debilitating symptoms. Among them, hematuria is the most common presenting symptom occurring in approximately 85% of diagnosed cases. Beyond the tumor mass, side effects of radiation or upper urinary tract neoplasms may be further reasons for bleeding. Sometimes hematuria may be difficult to control, incurable by irrigation or hemostatic trans-urethral resection, and thus is potentially life threatening. Furthermore, the recurrence of gross intractable hematuria is a significant concern, worsening the quality of residual life. Thus, SRC with a palliative intent may be an effective treatment of choice.

Zebic *et al.*^[25] carried out seven SRCs with a palliative intent, namely the surgical indication was due to T4a bladder cancer (3 patients) and pelvic malignancies leading to severe voiding symptoms, pain, and hematuria with need for repeated blood transfusions. Among them, 3 patients were lost during follow-up, 2 patients died during recovery for complications, and 2 patients lived 366 days after surgery. The preoperative risk was assessed by ASA score, resulting 4 patients ASA 4, two ASA 2, and one ASA 1.

Nagele *et al.*^[26] investigated clinical outcomes of 20 patients, with a mean age of 64 years, undergoing SRC for T4-stage bladder cancer. After a mean follow-up of 13 months (range 1-36 months), 11 patients were still alive. The authors reported only one lethal complication, namely an enterocutaneous fistula occurring during recovery. No data on preoperative surgical risk were reported.

The study of Cochetti *et al.*^[27] included 12 patients who underwent RC for massive hematuria due to bladder cancer and causing severe anemia (Hb level < 8 g/dL). The pathological exam showed pT4 stage in 6 patients, 2 patients with pT2, and 4 patients affected by pT3 stage disease. Major complications occurred in 18.5% of cases, while no deaths were recorded. Although all patients were defined as ASA 4, the mean Charlson Index was 6 and median Karnofsky scale was 85. An ileal conduit was used as a urinary diversion in all studies mentioned above, while ureterocutaneostomy was performed in the presence of severe comorbidities and poor performance status.

Thus, the studies all showed that, if technically feasible, in patients with a decent frailty status and accepting surgery, the future problems of bleeding may be completely obviated. Frailty is a new concept introduced to

estimate the patient's vulnerability to stress factors such as surgery. It has been recently developed in the context of bladder cancer because of the patient's median age at diagnosis, which makes the presence of several comorbidities highly probable^[28]. Although a variety of methods are available to measure frailty, a poor score has usually been associated with worse postoperative outcomes in patients who undergo urologic surgery including RC^[28].

When SRC is not possible due to the patient's elevated frailty status or the patient's refusal, several alternatives to a radical treatment have been proposed.

Since 1960, low-dose RT has been adopted to control hematuria. Regarding treatment outcomes, at 2 weeks, the rate of efficacy in arresting bladder bleedings has been reported as 60%-69%, while the risk of recurrence at 6 months has been computed as 33%-69%^[29-31].

Selective angiography for bladder embolization showed a high success rate (82%-100%) with complete cessation of hematuria within 48 h and a bleeding recurrence risk of 28%-50% within 16 months^[32]. However, this option is not free from complications. Ischemic pain, bladder necrosis, bladder infarction, and even inadvertent occlusion of uninvolved vessels by refluxed embolic material have been reported^[33].

Finally, several endovesical agents have been used to stop bladder bleeding such as 1% silver nitrate or 1%-2% alum and formalin (2.5%-4% for 30 min) with response rates of 71%-100% and 5%-100%, respectively. However, the treatment lasted 1-5 days, and in all cases anesthesia was required.

Salvage radical cystectomy: morbidity and mortality

SRC is thought to be difficult because of previous radiotherapy. Pelvic RT results in tissue damage that can also affect surrounding organs and lead to desmoplastic reaction, obliterating the tissue plane. This makes it difficult to identify and dissect surgical structures^[34].

By researching studies only using Clavien-Dindo system to grade complications, we found three single-institution studies^[5,35,36] which assessed complications of SRC after RT for MIBC and one multicenter study^[37] where SRC was carried out after RT for further diseases [Tables 3 and 4].

Gontero *et al.*^[37] retrospectively analyzed data from 25 large-volume institutions, defined as more than 30 cystectomies per year. Although only 27% of patients previously received RT for bladder cancer, the authors showed that the SRC is associated with a high risk of morbidity (75% risk of a single complication and a 33% risk of a major complication) and a 3.1% mortality rate at 90 days after surgery. Only large-volume centers participated in this study. Surgeon volume had a greater impact on outcomes in RC when compared with other surgeries such as lung resection for cancer, abdominal aortic aneurysm repair, and coronary artery bypass^[38]. Furthermore, it has been computed that more than 20 RCs per year positively affected the complication rates when compared to a lower number^[39].

Iwai *et al.*^[35] compared complication rates in patients with and without previous TMT using the standardized Clavien-Dindo grade. Data analysis showed that previous chemoradiotherapy increases the risk of urinary anastomosis-related complications (such as stricture and urinary leakage) and is associated with gastrointestinal complications (such as bowel perforation and Grade 3 ileus).

Table 3. Studies on complications after salvage radical cystectomy

Ref.	N of patients undergone to SRC	Findings
Iwai <i>et al.</i> [35]	87	40 Gy administered. Retrospective in nature comparing 87 SRC vs. 106 RC Urinary anastomosis-related complications and major gastrointestinal complications, most of which were Grade 3 ileus, were more frequent in the SRC respectively: 11% vs. 2%, $P = 0.007$ and 14% vs. 4%, $P = 0.002$
Eswara <i>et al.</i> [5]	91	Induction RT dose 40 Gy + 25 Gy consolidation in case of positive initial response Major complications, CCS ≥ 3 , occurred in 15 patients (16%). The overall 90-day complication rate was 69%. Perioperative mortality rate within 90 days was 2.2%
Eisenberg <i>et al.</i> [36]	148	Radiotherapy by 70 Gy. 90-day overall complication rate was 77%. Among them, 44.6% were low grade and 32.4% high-grade. The type of urinary diversion was not related to complication occurrence
Gontero <i>et al.</i> [37]	682	Retrospective in nature from SRCs carried out in 25 high volume centers (more than 30 procedures per year). Overall rate of complications was 75.1%; CCS ≥ 3 in 29.6% and CCS = 5 in 2.9% of patients. 27% of patients received RT for bladder cancer. Mean RT dose was 63 Gy (51-70)

RC: Radical cystectomy; SRC: salvage radical cystectomy; RT: radiotherapy; CCS: Clavien Classification System.

Table 4. Reported range of complications graded by Clavien-Dindo System

	Grade ≥ 3	Grade < 3
Infection (wound, urinary tract, others)	3-7	4-43
Gastrointestinal (ileus, bowel perforation)	8-14	10-17
Urinary anastomosis-related (leakage, stricture)	2-5	3-7

According to the authors, these complications would result, at least in part, from compromised blood supply to the tissue because of previous RT. Most patients (84%) received an ileal conduit as a urinary diversion, while the others received orthotopic ileal neobladder (6%), Indiana pouch (3%), or ureterocutaneostomy (7%). When univariate analysis was carried out to identify risk factors associated with urinary and bowel complications, the type of urinary diversions was not a predictor.

Eisenberg *et al.* [36] reviewed clinical data of RCs performed in their tertiary referral care center. In 148 patients who underwent SRC, they computed a 32.4% rate of high-grade complications (CCS ≥ 3). Again, ileal conduit was the most used urinary diversion (43.9%), and this was not related to the occurrence of complications, while ASA score and patients age were predictors.

Finally, in the study by Eswara *et al.* [5], which included 192 SRCs, major complications, Grades 3-5, occurred in 15 patients (16%) for a total of 23 events. The perioperative mortality rate within 90 days was 2.2%. Ileal conduit was the only used urinary diversion. However, the main finding of their study was to stratify complications occurrence by the date of SRC. Although there were no significant differences in the number of total complications, tissue healing-related complications occurred nearly three times more frequently (35% vs. 12%, $P = 0.05$) in the case of late SRC, namely disease recurrence after a mean of 10.3 months (range 2.1-178 months) from TMT termination. This group of complications included wound infection, ureteral stricture, anastomotic stricture, and stoma/loop requiring revision. Again, the authors explained this finding by assuming the higher dose (mean 64.7 Gy vs. 39.9 Gy) of radiation received.

All these studies reported occurrence of urinary anastomosis-related complications and major gastrointestinal complications more likely in the case of a previous radiotherapy that presumably caused an endarteritis process with subsequent ischemia delaying wound healing [40].

CONCLUSION

Salvage radical cystectomy is performed both after failure of conservative treatment for muscle invasive bladder cancer and as a palliative surgery in the case of intractable and fatal complications such as hematuria. An appropriate selection of patients suited for TMT leads to acceptable outcomes, whereas the rate of major complications ($CCS \geq 3$) in the case of a subsequent SRC is higher than the one previously reported for RC^[41]. Furthermore, during patient counseling for TMT, the high probability of receiving an incontinent urinary diversion in the future instead of an orthotopic neobladder in the case of immediate RC should be underlined. In the absence of comparative studies able to identify risk factors for TMT failure, a multidisciplinary cooperation and close follow-up is required. Likewise, SRC for symptom relief should be considered only if there are no other options and after an accurate assessment of patient frailty through the currently available questionnaires such as ASA score Charlson Index, Karnofsky scale, and Geriatric-8 currently able to estimate patient's vulnerability to stress factors such as surgery.

DECLARATIONS

Authors' contributions

Data research and manuscript drafting: Cicione A, Lombardo R, Voglino OA

Manuscript revision: Tubaro A, De Nunzio C

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Review

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Total extraperitoneal hernia repair and its associated pitfalls

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Abstract

Minimally invasive surgery over the last three decades has provided a credible alternative for the treatment of inguinal hernias. One of the main techniques involved utilises the creation of an extraperitoneal space, thereby avoiding the need to enter the abdominal cavity. The totally extraperitoneal (TEP) inguinal hernia repair is described as well as the common and more serious complications that are possible. TEP has a proven track record of expertise for the surgical treatment of inguinal hernias, but has a steeper learning curve, with more serious complications such as vascular and bladder injuries, which are explored in more detail. The key to managing any such serious complications is early recognition. Rectus sheath hematomas secondary to inferior epigastric artery injury usually require only conservative measures such as close observation with the requirement for any embolization of any arterial bleed a rare event. Bladder injuries if recognized at the time of surgery require immediate repair, with late presentation inevitably needing more invasive intervention for a potentially septic patient. TEP remains an excellent repair with caveats of serious complications which are rare at < 0.5% however, they must be discussed and be part of the consent process prior to any repair taking place.

Keywords: TEP inguinal hernia, complications of TEP, bladder injuries, inferior epigastric artery injury, rectus sheath hematoma, bruising, chronic pain



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INTRODUCTION

Inguinal hernias are a common problem worldwide and have a prevalence of 1.7% in the adult population. This rises to 4% in patients aged over 45 years as their incidence increases with age and they constitute 75% of all abdominal wall hernias^[1]. It affects men more commonly than women (lifetime risk 27% in men and 3% in women)^[1,2]. Surgical management is advised to reduce the complications associated with inguinal hernias including strangulation and subsequent bowel obstruction. Hernia repairs were commonly carried out using Lichtenstein or plug repairs but with the advent of minimally invasive techniques, laparoscopic repairs are becoming more common, more so, over the last two decades. In 2015, the Swedish Hernia Registry reported that 28% of inguinal hernias were repaired using minimally invasive surgery and 64% were using a Lichtenstein hernioplasty^[3].

Several studies have demonstrated the advantages of laparoscopic repair over conventional open repair techniques, including reduced post-operative pain and a shorter recovery time^[4-6]. The abdomen can also be examined for other unsuspected hernias, such as femoral hernias in women. However, there is an associated longer learning curve and a greater risk of intra-operative complications with the laparoscopic approach^[7]. Laparoscopic repair is more commonly used for the repair of bilateral inguinal hernias and recurrent hernias, as well as recently increasingly for some specialised hernias such as a sportsman's hernia^[8].

The two widely used laparoscopic techniques are trans-abdominal peritoneal repair (TAPP) and totally extraperitoneal (TEP) repair. Despite some clear advantages over open repair, laparoscopic techniques have associated complications, which are not seen with traditional open repairs^[9]. The recognised learning curve for both minimal access methods invariable remains steeper, with TAPP shown to be marginal as quicker to learn than TEP, due to the latter's increased dissection in the extraperitoneal plane which is required, but both have the risk of visceral & vascular injury, albeit small. But in TAPP as the peritoneal cavity is entered it has the additional risks of adhesions, small bowel injury as well as the risk of port-site hernias over TEP (0.27% vs. 0.1% for TEP)^[10-12]. Some reports suggest that for TEP the learning curve is between 50 and 100 cases to gain full proficiency of the operation as well as the ability to deal with complications^[13]. In this review, we will focus on TEP repair and its complications.

TECHNIQUE

TEP hernia repair involves a transverse incision lateral to the umbilicus, followed by identification and an incision of the anterior rectus sheath to identify the rectus muscle, which is then retracted to expose the posterior rectus sheath on the affected side. Above the posterior rectus sheath, the retromuscular/preperitoneal space developed and entered using a balloon trocar or blunt port, confirming its position with the camera^[8]. The balloon trocar is moved laterally, back and forth, opening up the Retzius space and Bogros' space laterally. Once the pre-pneumoperitoneum has been established, two 5 mm ports are inserted in the midline above the pubic symphysis and blunt dissection is carried out from the midline, lateral and below the inferior epigastric vessels and to the level of the anterior superior iliac spine to the pubic bone inferiorly (Cooper's ligament). The triangle of doom is exposed by retracting the peritoneum, the hernia sac dissected off the cord structures, and the vas deferens and testicular vessels are elevated. The indirect hernia sac and any significant cord lipoma are reduced and there should be a wide view of the pubic tubercle, and the insertions of the conjoint tendon and rectus muscles^[7,8]. A polypropylene or other synthetic lightweight mesh is placed flat over the dissected area, above the defect to Cooper's ligament and across the midline, covering the regions of direct, indirect (myopectineal orifice), femoral and obturator hernias^[14]. In a bilateral inguinal hernia repair, the same dissection is undertaken on the contralateral side with another mesh placed ensuring an overlap is achieved with the first mesh in the midline over Cooper's ligament. Methods for fixation include metal tacks, absorbable tacks, no fixation, sutures, self-fixating mesh

or tissue glue. Glue or atraumatic mesh fixation has shown to have a lower risk of complications such as nerve injury but especially both short- and long-term, chronic groin pain^[15]. The pre-peritoneum is then reduced, and the skin is closed using absorbable sutures^[7,8]. Patients are usually discharged the same day or the following day.

COMPLICATIONS

Immediate complications that are possible at the time of surgery include visceral injury (bowel and bladder), vascular injury, injury to the vas deferens as well as the spermatic cords. Immediately after surgery, patients can experience wound complications, bruising, scrotal swelling, seroma formation and hematomas. Delayed or late complications include adhesions (to mesh as well as adhesional bowel obstruction), fistula formation, testicular atrophy, nerve entrapment, and incisional hernia or a recurrence as well as chronic pain^[7,14,16].

With seroma formation, urinary retention can also be a problem seen post hernia repair, but this is more likely in older male patients secondary to prostatic hypertrophy. The incidence of post-operative urinary retention varies from 1%-3% and other risk factors as well as increasing age > 60 years including a history of benign prostatic hypertrophy, previous bladder neck surgery and an anaesthetic time of greater than 2 h^[16]. The incidence of seroma formation following laparoscopic repair is 5%-7% and is more common following dissection of both large indirect & direct hernias, especially L3 & M3 hernias (as per the EHS classification of groin hernias). Seromas will often resolve with time and do not require aspiration unless there are signs of infection or discomfort^[16].

Peritoneal injuries

Incorrect placement of the balloon trocar or simply sometimes dissection of the hernial sac may result in a breach of the peritoneum [Figure 1A], causing a pneumoperitoneum. Small peritoneal defects can be closed using a variety of methods; suturing, the use of clips [Figure 1B], or Endoloops. Closing the peritoneal defect avoids the loss of CO₂ into the peritoneal cavity, and therefore allows the preperitoneal workspace to be maintained.

Larger peritoneal tears essentially may force conversion to a TAPP repair, and thus is associated with the risks of a TAPP including visceral injury, adhesions, and port site hernias^[11].

Vascular injuries

Vascular injuries can occur with laparoscopic TEP repair as the inferior epigastric artery, external iliac vessels, corona mortis as well as spermatic cord vessels are all exposed during surgery. Any vascular injury occurring during hernia surgery can often lead to conversion to an open procedure albeit this is a rare event. The inferior epigastric artery is the most frequently injured vessel, which can be damaged by balloon dissection or using the camera to create the preperitoneal space [Figure 2A]. Most bleeding can be controlled using clips or cautery. Inferior epigastric arteries can be ligated by the use of clips at the time of surgery especially if inadvertently damaged, otherwise, there is always a risk of a significant retro-rectus hematoma. If such a hematoma develops and it is not causing pain or discomfort, then simple monitoring is adequate, otherwise surgical exploration may be required especially if acute and expanding, which can involve further laparoscopy, or a laparotomy as needed. If an acute hematoma does require surgical intervention, then it is recommended that the inferior epigastric vessels are ligated as these are the most likely sources of the bleed.

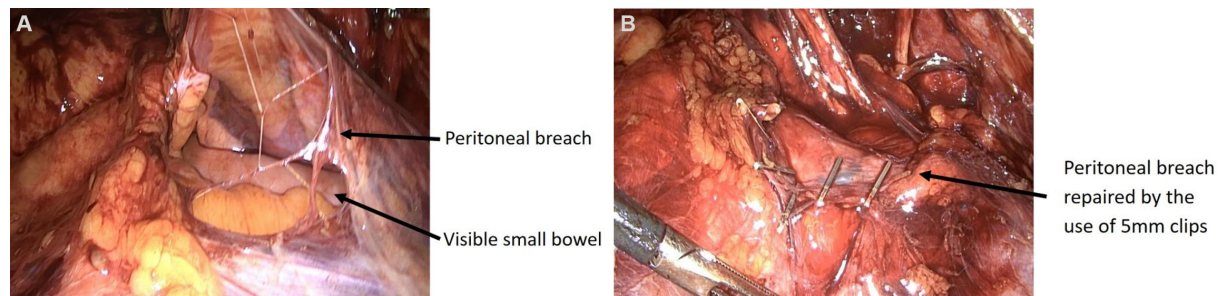


Figure 1. Peritoneal breach showing underlying small bowel during dissection for a right inguinal TEP repair (A). Peritoneal breach repaired by the use of 5 mm endo-clips (B). TEP: Totally extraperitoneal.

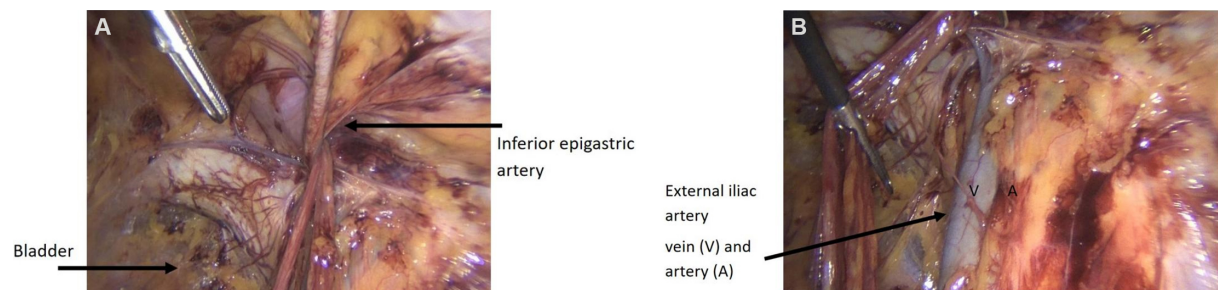


Figure 2. (A) Image showing TEP dissection and sites of possible injury with the inferior epigastric artery and the bladder. Inferior epigastric artery can cause a rectus sheath hematoma. It should be clipped if injury is inadvertently caused. (B) Image depicting the external iliac vessels, injury to these most likely will require intervention by vascular surgeons. TEP: Totally extraperitoneal.

An acutely diagnosed bleed, within the first 6 h of surgery, should therefore be assessed with CT imaging with contrast and any bleeding vessel can be subjected to arterial embolization to control a side branch bleed, which is largely very effective with experienced vascular radiology expertise availability.

Late presentations such as rectus sheath hematoma are usually due to a small bleed from a branch of the inferior epigastric artery or vein [Figure 2A]. These normally required no further intervention, will present with a painful rectus sheath hematoma which is diagnosed after imaging and can be managed with embolization of the vessel in the acute phase. More serious injuries will be to the external iliac vessels [Figure 2B], which will require early or immediate vascular surgical intervention.

Ischaemic orchitis can be caused by injury to the vas deferens or spermatic vessels, resulting in testicular atrophy, chronic testicular pain, or retrograde ejaculation^[16,17]. It presents with painful testicular inflammation in the first 5 days post-operatively, with an incidence of 0.05%-0.1% in patients with large inguinoscrotal hernias. Treatment is with anti-inflammatories and scrotal suspension.

Bladder injuries

Injury to the bladder during TEP repair is rare and has a reported incidence of less than 0.5% but it lies in an anatomically vulnerable position and is easily seen during this operation lying below the ilio-pectineal (cooper's) ligament [Figure 2A]^[18,19]. Bladder injuries are most likely to occur during port placement, or when dissecting a large direct hernial sac. The injury is usually recognised when urine is seen in the extraperitoneal space and it is therefore important that patients empty their bladder completely prior to surgery to reduce this risk as a full bladder will not only prevent dissection but be more prone to injury. Bladder injuries can often be repaired endoscopically using a one-layer or two-layer approach for a visible

injury^[19] and a urinary catheter is left in situ for 5-10 days^[16]. If a bladder injury is noted at the time of initial dissection, it is recommended that the repair is undertaken at the time, with the help of a Urologist if possible recommended. Surgery can of course be completed, and a check cystogram should be undertaken on at least day 10 prior to removal of the catheter. It is important to consent all patients for the risk of bladder injury prior to the operation.

Steps for managing inadvertent bladder injury at the time of TEP repair:

- (1) Do not panic;
- (2) Seek urology advice;
- (3) Place an extra 12 mm port to aid in introducing 2/0 needles and suturing the bladder defect;
- (4) Double layer repair with the introduction of a urinary catheter under the vision;
- (5) 100 mL of saline used to inflate the bladder under vision to check a water-tight repair;
- (6) Complete surgery and check cystogram after 10 days prior to catheter removal.

If a bladder injury is not recognised at the time of surgery patients will normally re-present early with severe lower abdominal pain, haematuria, rising inflammatory markers, sepsis with CT imaging identifying pre peritoneal fluid. It is very difficult to reattempt laparoscopic surgery, although not impossible, but a laparotomy may be inevitable with subsequent bladder repair and urinary catheterization for 10 days. Describing a spectrum of complications from TEP repairs this would be one of the more serious sequelae as well as an unrecognized bowel complication requiring a laparotomy, normally as a result of an unrecognized breach of the peritoneum, allowing small bowel to adhere to the mesh.

Mesh complications (bladder)

The use of prosthetic mesh is becoming increasingly common in hernia repairs, and therefore complications with mesh migration or mesh erosion albeit rare, have also been reported. Both TAPP and TEP hernia repairs are associated with mesh erosion into the bladder and can occur anywhere between 3 months to 10 years post-operatively^[20]. Cases of mesh erosion into the bladder usually require re-operation and mesh removal, and in some cases a partial cystectomy, but this event is extremely rare and may be associated with an increased risk if previous pelvic surgery has been undertaken prior to the hernia repair.

Chronic pain

Pain that persists for longer than 3 months after surgery and is defined as “chronic post-operative inguinal pain (CPIP)”. It can be categorised as bothersome moderate pain impacting daily activities lasting at least 3 months post-operatively and decreasing over time^[6]. The incidence of chronic groin pain following TEP repair is much less than an open repair^[16,21]. Mesh fixation using staples or tacks, however, increases the risk of chronic groin pain.

Patients that suffer complications are more likely to experience chronic groin pain. Although the chronic pain incidence is low, there are potential consequences with neuropraxia to the ilioinguinal, iliohypogastric nerves and even the genital branch of the genitofemoral nerve. The latter is one of the most commonly affected nerves in laparoscopic surgery as well as the lateral cutaneous nerves of the thigh. Patients present with an area of numbness just below the mid inguinal point on the thigh and should be managed with nerve pain killers and physiotherapy. The lateral cutaneous nerves of the thigh are more likely to be injured if dissection of the fascia is too close to these nerves laterally or by peeling the peritoneum too close to the lateral muscles on initial dissection. The lateral cutaneous nerves can be seen in very thin patients and should always be preserved with any subsequent damage presenting with pain on the lateral aspect of the

affected thigh. Sometimes as a result of the use of traumatic fixation pain can also be caused in this area and if the pain occurs immediately after surgery, it is recommended that the patients are taken back to the theatre to remove the tacks. This manoeuvre does not avoid the complete effects of nerve damage, but it may abate the severity of the injury.

Nerve injuries described above do require careful evaluation by a groin specialist, nerve mapping, magnetic scan with neurography, with possible re-exploration and subsequent division of the nerves, but only after a failure of nerve painkilling agents, and desensitisation treatments including physiotherapy.

Surgical emphysema

This can occur after surgery especially with the TEP procedure. The extraperitoneal space that is created can allow gas to escape into this space further up the torso, with some patients experiencing even neck and facial pain because they have surgical emphysema, which is easily palpable. This complication does disappear eventually in time, reassurance and painkillers are all that is needed if the patient remains systemically well. Patients should be able to carry on normal bodily functions, daily activities and early follow up in the clinic after 5 to 7 days is all that is required.

DISCUSSION

Totally extraperitoneal repair for inguinal hernia remains a fast-growing procedure. It initially drove up the cost of the operation. However, with increasing expertise, experience, utilisation of cost-effective resources and most importantly its inception reducing the length of stay, recovery and return to normal activities has overall provided patients and healthcare with good benefits. The main caveat with any hernia surgery is of course the risk of complications and the TEP repair does rely on increasing expertise, with a recognised steeper learning curve^[9]. Like any surgery, the consent process has profound implications on the direction a surgeon wishes to steer their patients in terms of which operation they will choose. Options should though always be given to patients especially with bilateral or recurrent hernia to undergo a minimally invasive technique. This has been shown in international and NICE guidelines^[9,22]. Understanding the caveats in any surgical procedure are though profoundly important, especially in modern-day practice. The majority of patients will thankfully not experience any serious complications however, the more common ones associated with this repair would include umbilical wound infections, heavy bruising across the abdomen, early surgical emphysema, penile and scrotal swelling for male patients, which all generally subside within two to three weeks after the repair. Some patients will have debilitating seromas which require aspiration but again these are few and far between. Any more serious complications such as identification of vascular or bladder injuries at the time of surgery should be managed with at this time and by the utilization of specialist expertise if required. An unrecognised bladder or bowel injury will present with abdominal pain, sepsis, haematuria and rising inflammatory markers a few days after surgery. These are the most serious of risks that all patients should be advised of as part of the consent process, but a bladder injury if recognized, subsequently suture repaired with the placement of a urinary catheter should not cause undue long-term harm to a patient other than the discomfort of a urinary catheter for 10 days. Rectus sheath hematomas are managed conservatively with arterial embolization of any injury to the inferior epigastric artery rarely required but remaining a possible feasible treatment modality.

Overall, the morbidity associated with the TEP inguinal repair operation is small with only 5%-10% of patients experiencing a minor complication such as bruising, or wound infections, which all require reassurance and monitoring. It is only the serious complications, which surgeons should be aware of and their incidence is less than 0.5%.

Opponents of minimally invasive surgery will inevitably cite these risks with potentially serious complications as reasons not to engage in such techniques where open suture or mesh surgery is safe and just as effective. But in safe hands and adherence to a careful training module, such complications are rare with most patients recovering more quickly with an earlier as well as less painful return to normal activities and work.

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Authors' contributions

Made substantial contributions to the design, literature review and writing of this manuscript: Alam N, Sheen AJ

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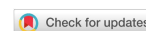
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Editorial

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The future of robotic radical prostatectomy driven by artificial intelligence

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Since we have entered the precision prostate cancer surgery era^[1], the robotic approach currently represents the preferred choice of the patients^[2]. Focusing on robot assisted radical prostatectomy (RARP), several technical^[3-5] and technological^[6] innovations have been introduced with the aim to maximize both functional and oncological outcomes.

The advent of three-dimensional (3D) technology^[7] meets both patients'^[8] and surgeons' preferences^[8,9], allowing visualization of the anatomy three-dimensionally and enhancing the perception of the disease's location and characteristics, such as its relationship with the prostate capsule.

A step further in this direction is represented by the possibility to overlap the 3D virtual images with the real anatomy during *in vivo* robotic procedure, performing augmented reality procedures^[10,11]. As reported in our previous experiences, 3D prostatic models can be obtained from 2D-MRI images and consequently used during RARP, allowing the surgeon to focus on the tumor's characteristics, with particular attention to the potential presence of extracapsular extension. Thanks to specifically developed software, virtual models can be displayed on the da Vinci surgical console (Intuitive Surgical Inc.) and automatically anchored to the *in vivo* live images during surgery^[12].



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Notwithstanding the initial encouraging findings, this approach revealed not to be accurate enough due to the high heterogeneity of colors displayed during the endoscopic view and the absence of clear intraoperative landmarks for providing a precise spatial orientation along the three main axes. In the current year, we began to explore the potential applications of artificial intelligence (AI) for urologic *in vivo* surgery. Our new approach consists of a two-step automatic system that aligns a 3D virtual model of the patient's prostate with the endoscopic 2D images at the end of the extirpative phase during RARP. For each of the two steps, a specific convolutional neural network (CNN) was developed. Briefly, the first CNN outputs catheter location and z rotation by identifying the anchor point. The second CNN returns antero-posterior rotation on the x axis. Their combined results allow to perform the actual overlay rate. Our findings are promising and were presented during the last edition of Virtual EAU 2021, showing that the introduction of CNNs allows to correctly overlay 3D virtual images in a completely automatic manner. The correct identification of extracapsular extension at the level of the resection bed can potentially bring a reduction in positive surgical margins rates, with a subsequent oncological advantage for the patients with locally advanced disease^[13].

As shown in the recent literature, the application of AI in uro-oncology has gained wide diffusion^[14]; despite its use during live surgeries, it is still limited to anecdotal experiences^[15]. The intraoperative support of machine learning (ML) for autonomous camera positioning was promisingly explored analyzing data obtained by instrument kinematics, laparoscopic video, and surgeon eye-tracking^[15]. On the contrary, the application of ML to more complex tasks (e.g., suturing, knot-tying, and tissue dissection) is more difficult to reach. As recently summarized by Ma *et al.*^[16], a robot must be able to perform three different actions to complete these surgical tasks: it must “see” (vision recognition), “think” (task planning), and “act” (task execution).

Therefore, even if this field of research seems to be the most appealing, we need to think of the potentiality of AI driven surgery, looking to a wider horizon^[16,17].

Starting from preoperative setting, as shown by Auffenberg *et al.*^[18], specifically developed ML algorithms can help the surgeon in selecting candidates for the different treatments (e.g., active surveillance, radical prostatectomy, radiation therapy, and androgen-deprivation therapy) by analyzing data from the electronic health records.

Furthermore, this technology may also be applied for improving surgical training: by extracting data from the da Vinci console, dedicated ML can be developed to automatically analyze the trainees' movements, providing a personalized evaluation highlighting the strongest and weakest technical abilities^[19]. As well, the application of ML-based analysis to automate segmentation of anatomical landmarks during 12 different surgical steps during RARP showed, with respect to human segmentation, that the ML-based model annotated better the boundaries^[20].

Looking to the future, the further development of robotic technology towards automation will enhance surgical outcomes by improving the workflow and minimizing repetitive or mundane tasks^[21].

However, the most challenging aspect of this technology is the ability to reproduce the sophistication of human movements and therefore to reach complete autonomy.

Theoretically, to reach this quality of information, multiple tertiary centers should provide standardized data, following uniform standards. Deep learning models developed from these data may be able to predict unexpected complications, offering the surgeon a chance to adjust the intraoperative planning. The robotic system would also be able to recognize the operator and adapt its feedback to the surgeon, providing instantly tailored data to reach the best and smartest surgical decision making^[16]. Moreover, exploiting the available cloud services and high-speed internet connection (i.e., 5G), information can be rapidly exchanged between machines.

Even if this scenario sounds appealing, the assurance of data secrecy and the lack of precise legislation represent technical obstacles which still need to be overcome.

In conclusion, particularly in an intraoperative setting, the advent of AI is obstacle by the lack of live data collection and by the complexity of privacy and data sharing legislation.

For all these reasons, the current research should be focused on the ability of AI to provide the operator important additional information (e.g., augmented reality images) during the surgical procedure, rather than trying to substitute the surgeon.

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Case Report

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Retroperitoneoscopic single-site 3D adrenalectomy for left adrenal renal cell carcinoma metastasis 20 years after left laparotomic radical nephrectomy

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Abstract

The aim of the paper is to demonstrate the practicability of retroperitoneoscopic single-site 3D left adrenalectomy after previous homolateral laparotomic renal surgery. We present a case report of a 70-year-old male who underwent radical nephrectomy in 1999. Twenty years after radical nephrectomy, the patient underwent a computed tomography scan for B-cell lymphoma follow-up, which revealed a 30 mm left adrenal mass suspicious for a delayed renal-cell carcinoma metastasis. After multidisciplinary discussion, surgery was chosen as first option. To minimize surgical morbidity as much as possible, a 3D laparoscopic single-site retroperitoneal approach was chosen. The patient had no peri- or intra-operative complications and was discharged on Postoperative Day 3. The final histological report revealed an adrenal clear cell renal-cell carcinoma metastasis. This experience shows that single-site retroperitoneal laparoscopic adrenalectomy is possible in patients who underwent previous abdominal cancer surgery and is an option to consider when determining optimal approaches for adrenal surgery.

Keywords: Adrenalectomy, laparoscopy, laparoendoscopic single-site surgery, renal cell carcinoma metastases



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INTRODUCTION

Renal-cell carcinoma (RCC) accounts for about 2% of all cancers. Up to 30% of patients experience metastasis at diagnosis or during follow-up^[1]. The most common localizations of RCC metastasis are lung, liver, bone, adrenal, brain, and nodes. Late single metastatic RCC recurrence, more than 10 years after nephrectomy, in ipsilateral or contralateral adrenal gland is a rare event reported in 3% and 0.7% of remaining kidney units, respectively^[2]. In the case of single metastasis or recurrent disease, surgery can be considered as a treatment option in those patients who have a favorable risk profile and in whom complete resection is achievable^[3]. The surgical approach must be chosen according to the patient's characteristics, size of the lesion, and surgeons' expertise^[4]. Nowadays, minimally invasive surgery is the gold standard for the treatment of urological malignancies, and many techniques are being developed in order to reduce surgical morbidity as much as possible. In particular, laparoscopic adrenalectomy series in the literature show low morbidity and complication rates in addition to short hospital stays^[4]. Moreover, the retroperitoneoscopic approach and single-port approaches have shown equivalent or favorable perioperative outcomes to be a justified alternative for advanced surgeons^[3-4]. We present a case report of a 70-year-old male who underwent retroperitoneoscopic single-site left adrenalectomy for adrenal RCC metastasis 20 years after laparotomic adical nephrectomy for cell renal-cell carcinoma (CRCC).

The aim of our work is to show the practicability of 3D retroperitoneoscopic single-site retroperitoneal adrenalectomy after previous homolateral renal surgery.

CASE REPORT

We present a 70-year-old Caucasian male with a history of hypertension, benign prostatic hyperplasia, and previous B-cell lymphoma with negative follow-up. In May 1999, he underwent laparotomic left RN for a 10 cm CRCC of middle/lower pole of the left kidney with thrombosis of the left renal vein and peri-renal fatty tissue invasion (pT3b N0); no ipsilateral adrenalectomy was performed at that time due to surgeon's preference. The patient was thereafter followed for 10 years according to the renal cancer European Association of Urology (EAU) guidelines^[1]. In May 2019, due to a lateral cervical mass, the patient underwent left lateral cervical lymph node dissection with diagnosis of stage IA G3 B-cell lymphoma and was subsequently treated with local radiation therapy. In September 2019, a CT scan performed for routine lymphoma follow-up revealed an inhomogeneous left adrenal solid expansive lesion of 30 mm × 20 mm [Figure 1]. A multi-disciplinary meeting with hematologists, oncologists, and endocrinologists was scheduled, and indication to surgery, with diagnostic and curative intent, was proposed. In consideration of the previous surgery and of the localization of the mass, a retroperitoneal approach was chosen; moreover, the retroperitoneoscopic single-site technique was considered to reduce morbidity.

Surgical procedure

In November 2019, the patient underwent left retroperitoneoscopic single-site adrenalectomy. Utilizing a left lateral decubitus position, a 2.5 cm lateral incision was made [Figure 2] at the tip of the twelfth rib, through which a single-site gel port (GelPOINT® Advanced Access Platform, Applied Medical, Rancho Santa Margarita, CA, USA) was inserted [Figure 2]. The retroperitoneal operating space was created with an air inflating balloon as previously described^[5]. A standard 10 mm, 0-degree 3D laparoscopic camera [Image 1 S TM 3D (Karl Storz, Tuttlingen, Germany)] was used throughout the procedure in addition to standard and bent single-port laparoscopic 5 mm instruments. The caiman® 5 (Braun Vetcare, 78532 Tuttlingen, Germany) was used for dissection and vessel sealing. The adrenal gland was identified and bluntly isolated from the psoas, posteriorly and inferiorly from the colon. The left adrenal vein was identified, isolated, and secured using 5 mm polymer clips. The specimen was removed within a retrieval bag, and a 20-Fr drainage was placed in the lateral part of the incision [Figure 3].

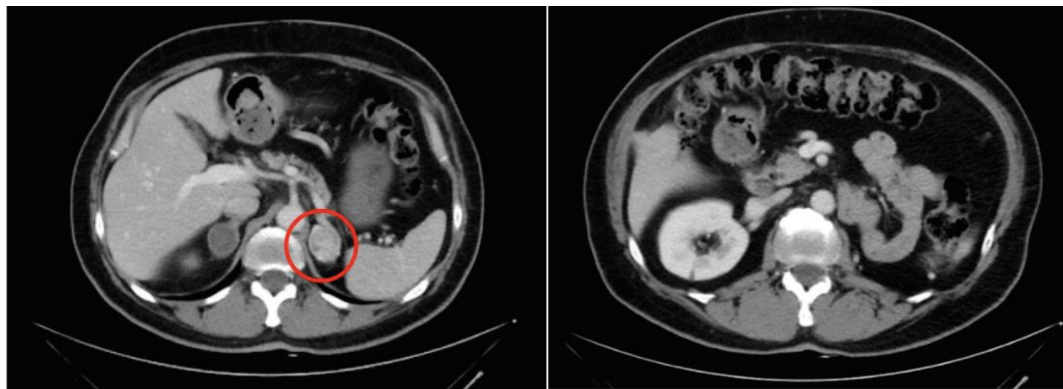


Figure 1. CT scan showing the adrenal solid expansive lesion (30 mm × 20 mm) mass and left empty renal lodge. CT: Computed tomography.



Figure 2. The 2.5 cm incision at the tip of the 12th rib and single-site gel port GelPOINT® Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA, USA).

Results surgical procedure

Total surgery time was 92 min. The patient had no perioperative complications and was discharged on Postoperative Day 3. The final histological report revealed an adrenal CRCC metastasis with positive immunophenotype for vimentin CD10, CAM5.2, and CKAE1/AE3 and negative immunophenotype for CK7, CD117, and inhibin.

DISCUSSION

CRCC metastases occur during follow-up in about 1/3 of patients^[2]. Typical locations of metastases are brain, lungs, bones, liver, and adrenals. The optimal treatment for locally recurrent RCC is still under debate, and, according to EAU guidelines, surgical treatment for recurrent disease must be offered when technically feasible, when complete resection of the mass is achievable, and in the lack of major comorbidities^[1]. However, in the era of targeted molecular therapies, surgical metastasectomy, when feasible, remains the gold-standard treatment, with five-year cancer specific survival of 60%^[3]. Indeed, systemic immunotherapies with interferon and interleukin-2 (IL-2), or more recent therapies with multikinase inhibitors (sorafenib, sunitinib, pazopanib, axitinib, lenvatinib, and cabozantinib), mTOR inhibitors (temsirolimus and everolimus), monoclonal antibody against the eGFR (bevacizumab), and immunomodulatory drugs (nivolumab, ipilimumab, atezolizumab, pembrolizumab, and avelumab), alone or in combination, have been shown to improve survival and oncological results with complete responses in less than 10% of patients and are burdened by frequent and occasionally severe toxicity^[6]. Moreover, many studies have shown a significant increase in cancer specific survival and median overall survival in patients

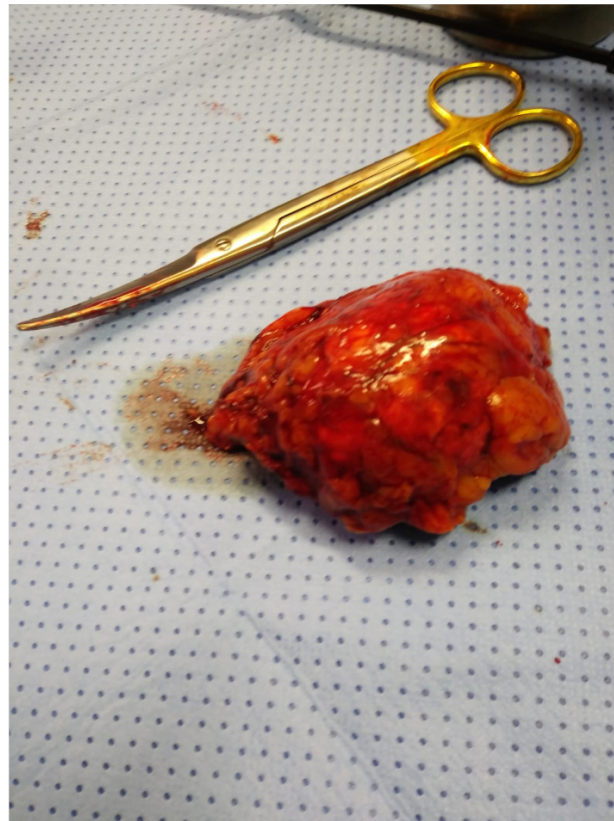


Figure 3. Adrenal specimen.

treated with complete metastasectomy compared with those in which surgery was incomplete or omitted^[7]. In the current paper, we present a very delayed onset of adrenal CRCC metastasis, 20 years after the removal of primary tumor. We chose to avoid biopsy because of the double usefulness of surgery as diagnostic and curative intent. Favorable predictors of survival after RCC metastasis resection are: (1) diagnosis to occurrence of metastases > 1 year; (2) a unique metastatic site; and (3) age < 60 years^[8]. Our patient presented with two out of three favorable characteristics. We planned to remove the adrenal mass with a single site laparoscopic retroperitoneal approach in consideration of the shape, position, and previous abdominal surgery.

Laparoscopic adrenalectomy was described for the first time in 1992 and has since become the most used approach representing the gold-standard treatment for adrenal masses due to low perioperative morbidity and low complication rates, offering reduced postoperative pain, length of stay, and recovery time^[9-11]. The following minimal invasive techniques have been described to approach the adrenal gland with laparoscopy and robotics: transperitoneal or retroperitoneal via the anterior or lateral approach and single-port transperitoneal or retroperitoneal. None of these techniques however have demonstrated a clear superiority, highlighting the importance of the experience of the surgeon and center^[4]. Comparable safety and outcomes have been demonstrated between transperitoneal and retroperitoneal laparoscopic approaches when performed by trained and skillful surgeons^[11-15]. The same is true for single-site laparoscopic surgery, where the choices of the technique and of the approach are made by the surgeon according to his skills.

Single-site laparoscopic adrenalectomy can be comparable to the multi-port approach, as trans-peritoneal is comparable to retroperitoneal^[16]. The advantages reported for single port surgery are lower blood loss, lower analgesic time, and improved cosmetic satisfaction against longer operative time. However, our operative time was lower or comparable to published results, and our perioperative outcomes, postoperative pain, length of stay, and recovery time were improved. When the diagnosis of adrenal CRCC metastasis was made, the case was discussed during the weekly multidisciplinary meeting with the oncology team, the endocrinologist, and radiotherapists, and the final indication was to continue with follow-up and not to perform immediate systemic treatments. The role of the multidisciplinary approach is pivotal in the tailored management of these patients.

Minimally invasive surgical approaches and techniques must be tailored case by case according to the facilities and skills of the surgeon and patient characteristics. In the current report, we show that single-site retroperitoneal laparoscopic adrenalectomy is a possible procedure for patients who underwent previous trans-peritoneal abdominal surgery and is an option to consider when determining optimal approaches for adrenal surgery. However, the retroperitoneoscopic single-site technique should be pursued only when it does not compromise the overall and oncological safety of the patient and the surgeon has the expertise to perform the procedure.

DECLARATIONS

Authors' contributions

Conceptualization, writing - original draft, project administration: Naspro R, La Croce G

Methodology, formal analysis: La Croce G

Data curation, writing - review & editing: Roscigno M, Pellucchi F, Lerner L, Rossini A, Cassibba S

Conceptualization, supervision: Naspro R, Da Pozzo LF

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

A written informed consent for publication was obtained.

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Review

Open Access



Hybrid coronary revascularization: the Emory experience

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Abstract

This article reviews the Emory University Experience with hybrid coronary revascularization and identifies key factors essential for the success of this relatively new and evolving strategy for the treatment of coronary artery disease. Key decisional and technical factors were identified. In addition, careful patient selection, stepwise progression in learning the different aspects of the procedure, and close collaboration between cardiac surgery-interventional cardiology are key factors for success.

Keywords: Hybrid coronary revascularization, robotic coronary bypass, robotic LIMA LAD anastomosis

INTRODUCTION

Hybrid coronary revascularization (HCR) has evolved over the past decade as a strategy for the treatment of multivessel coronary artery disease combining the most significant advantages of surgical coronary artery bypass (CABG) and coronary artery stenting in order to provide the best possible short- and long-term results with minimal invasion of the patient. The 88%-90% 20-year patency rate of left internal mammary artery (LIMA) to left anterior descending (LAD) coronary artery is the pinnacle of what CABG can offer and is hard to beat^[1-4]. This excellent patency rate translates into improved survival, improved relief of symptoms, decrease in major adverse cardiac events and decrease the need for reintervention^[1-4]. Equally important, even though CABG has better long term outcomes than percutaneous coronary intervention (PCI) for multivessel CAD^[5], the newer generation drug-eluting stents (DES) deployed to treat discrete



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lesions in non-LAD territories have excellent short term patency rates (6.6% target vessel failure at 8 months, 8.9% target vessel failure at 3 years)^[6,7] comparable or superior to vein grafts to the same territories (25% vein graft failure at 12-18 months)^[8] without the morbidity of CABG.

The hybrid strategy has a steep learning curve, particularly on the cardiac surgery side, because the LIMA LAD anastomosis is done without a sternotomy in an off-pump or beating heart fashion. The strategy also requires seamless teamwork between cardiac surgery and interventional cardiology.

The American College of Cardiology, American Heart Association, American College of Physicians, American Association for Thoracic Surgery, The Preventive Cardiovascular Nurses Association, The Society for Cardiovascular Angiography, and Interventions and The Society of Thoracic Surgeons have issued joint guidelines for HCR, defined as the planned combination of LIMA-to-LAD artery grafting and PCI of one or more non-LAD coronary arteries^[9].

Class IIa indications include limitations of traditional CABG (heavily calcified ascending aorta, poor non-LAD target vessels but amenable to PCI, lack of suitable graft conduits) and unfavorable LAD anatomy for PCI (chronic total occlusion or excessive LAD tortuosity).

Class IIb indications include attempts to improve the overall risk-benefit ratio of both PCI and CABG in patients who have multivessel coronary artery disease, would benefit from a LIMA to LAD bypass but have other comorbidities that put them at risk of complications after surgery (recent MI, frailty) or need a rapid return to baseline activities.

This article aims to distill the lessons that we have learned at Emory University over the past decade of application of this strategy and provide guidance on the steps required to introduce it into the armamentarium of an institution.

CABG WITHOUT STERNOTOMY (MINIMALLY INVASIVE CORONARY SURGERY)

Efforts to avoid partially or completely the sternotomy to perform CABG started in 1995 with Dr. Benetti^[10].

At Emory, we moved in the early 2000s to harvest the LIMA using video-assisted thoracic surgery techniques (VATS), a robotic arm, Aesop (Intuitive Surgical, Mountainview, CA) to hold the camera, and a 1.5-2-inch incision, if necessary with resection of costal cartilage, to perform the LIMA to LAD anastomosis off-pump, using a port-based cardiac positioner (Medtronic, Minneapolis, MN. Guidant, Santa Clara, CA, Estech, Danville, CA). The technique was called EndoACAB (endoscopic atraumatic coronary artery bypass). A significant experience of 607 patients was accumulated with excellent results: 30-day mortality of 1%, a mean ICU length of stay of 11.2 ± 9.9 h, a hospital length of stay of mean 2.4 ± 1.3 days, a conversion to sternotomy or standard thoracotomy of 3.6% (0.7% emergent) and 5-year survival of $92.9\% \pm 2.4\%$ ^[11].

Unfortunately, the VATS technique to harvest the mammary was difficult to learn, mainly because the LIMA was harvested with long-shafted instruments endoscopically. Such instruments amplify hand tremors and have no articulation of the distal ends of the instruments to allow complex intrathoracic manipulations. In addition, the Aesop robotic arm, essential for holding the camera, was unfortunately discontinued from production. Furthermore, the advent of the robotic Da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) made this procedure somewhat obsolete.

The Da Vinci robot introduced a new level of precision, visualization, and endoscopic freedom of movement inside the body with 3-dimensional articulating instrumentation and 10x high fidelity magnification. Thus, exposure and visualization were greatly facilitated, and more complex movements could be made inside the chest. Furthermore, the 3-dimensional wristed instruments provided a greater range of motion in a small space. In addition, the robotic instruments are able to filter the hand tremor; hence this becomes a non-issue. Finally, dual consoles allow the technique to be taught much more easily, with seamless transfer of controls between mentor and trainee.

The majority of minimally invasive CABG procedures since 2009 at Emory have been performed with robotic assistance, thus the term robotic-assisted CABG. The procedure has been extensively described in publications^[12-16]. Briefly, patients are placed supine on the operating table, and after induction, two rolled sheets or a bump is placed under the left shoulder with the superior tip of the bump placed just inferior to the scapula. The patient is positioned slightly towards the left of the table so that when the left arm is loosely tucked, the left shoulder gently hangs off of the bed. The lowering of the left shoulder is critical to avoid conflict with the robotic arms. The patient is then prepped and draped in the usual fashion for coronary bypass surgery; the middle of the chest is marked between the clavicle and costal margin [Figure 1]. There is no specific interspace, but the camera port should be generally placed in the middle of the chest or just slightly lower at approximately the anterior axillary line.

A spinal needle is used to identify the rib and the interspace. We always use a blunt instrument similar to tube thoracostomy prior to inserting the camera port. The camera port can then be placed gently with a slight angle superiorly to avoid underlying cardiac injury. Immediately after this port is placed, carbon dioxide insufflation should be initiated from 8-12 mmHg with careful attention to blood pressure while creating a tension pneumothorax. Not infrequently, anesthesiology will need to make adjustments with loading conditions to allow the patient to tolerate this. The insufflation can be adjusted up or down (6-15 mmHg) as needed. The camera is then inserted, and the superior port is placed 2 interspaces above the camera port in either the 2nd or 3rd interspace, more medial than the camera port.

The inferior port is placed 2-3 interspaces in a similar medial-lateral position as the camera port. Note, the working arm ports should be placed with endoscopic guidance so you can see where the ports are entering the chest and in which interspace [Figure 2]. Finally, the da Vinci system is docked [Figure 3], and the LIMA can be harvested as a thin pedicle or skeletonized.

Our preference is to remove the overlying muscle and fascia to expose the LIMA completely and then take the vessel as a thin pedicle with electrocautery and clips to avoid any manipulation of the artery [Figures 4 and 5]. A small pericardial window posterior to the phrenic is then made, the pericardial fat is dissected off the anterior pericardium, and a full longitudinal pericardiotomy is then made to mirror the same pericardiotomy that would be made via sternotomy [Figure 6].

After dividing the LIMA distally with clips, the robot is undocked, the endoscope and a spinal needle are used to help with localization of the skin incision so that after a 3-4 cm thoracotomy incision is made, the LAD target should lie directly underneath. No rib retractors are used, but exposure is usually more than adequate with a soft tissue retractor without dividing or resecting any ribs or costal cartilage. The Nuvo stabilizer (Nuvo; Medtronic, Minneapolis, MN) is used to stabilize the LAD; a vessel loop is placed around the more proximal LAD, and tests occluded for 3 min while the LIMA is prepared.

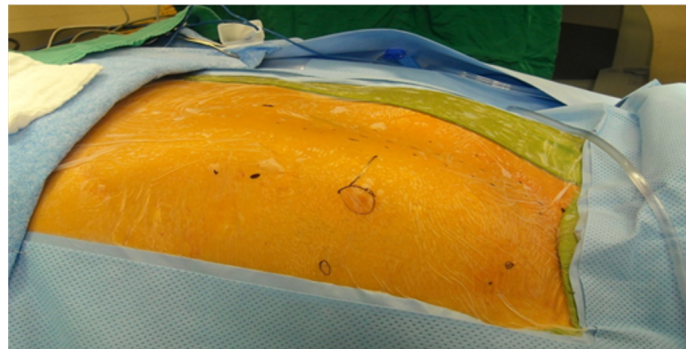


Figure 1. Robotic coronary artery bypass: planning of the incisions.

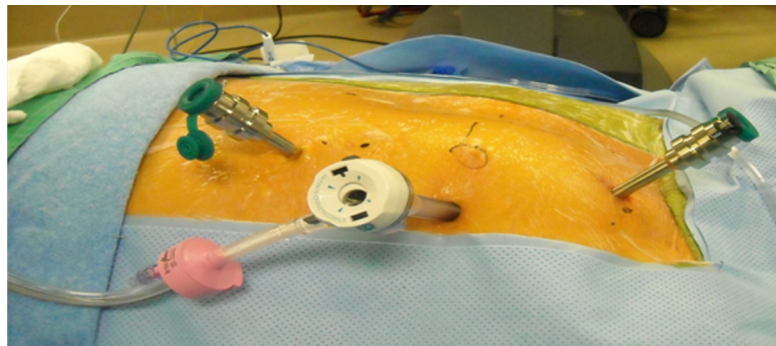


Figure 2. Robotic coronary artery bypass: port insertion.



Figure 3. Robotic coronary artery bypass: docking of the Da Vinci robot.

Then the anastomosis is done off-pump with a shunt in place in the same manner that would be done via sternotomy [Figure 7].

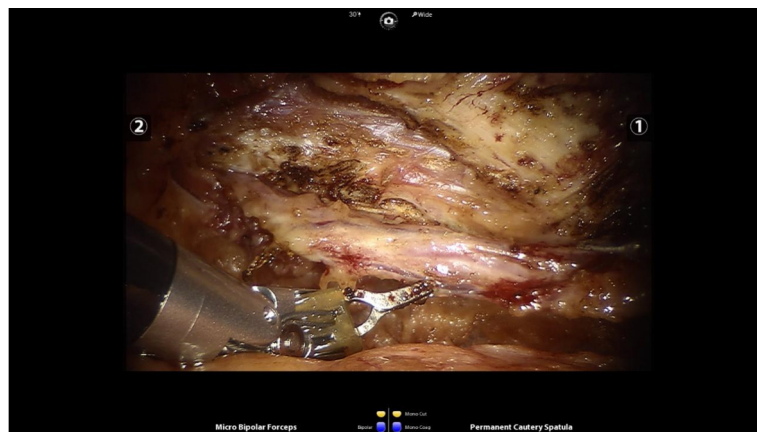


Figure 4. Robotic coronary artery bypass: starting the left internal mammary artery dissection.



Figure 5. Robotic coronary artery bypass: continuing the left internal mammary artery dissection.

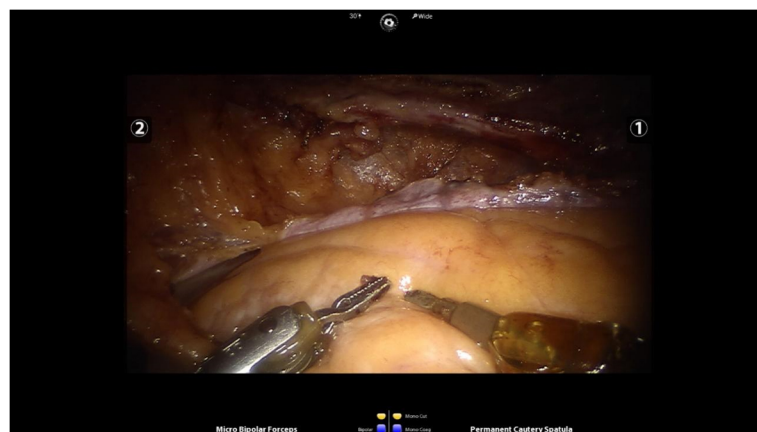


Figure 6. Robotic coronary artery bypass: identifying the left anterior descending.

The shunt decreases the risk of electrical or hemodynamic instability, which is a devastating complication in a case without ready access for cardiopulmonary bypass. Final angiographic results after completion of the HCR are presented in [Figures 8 and 9](#).

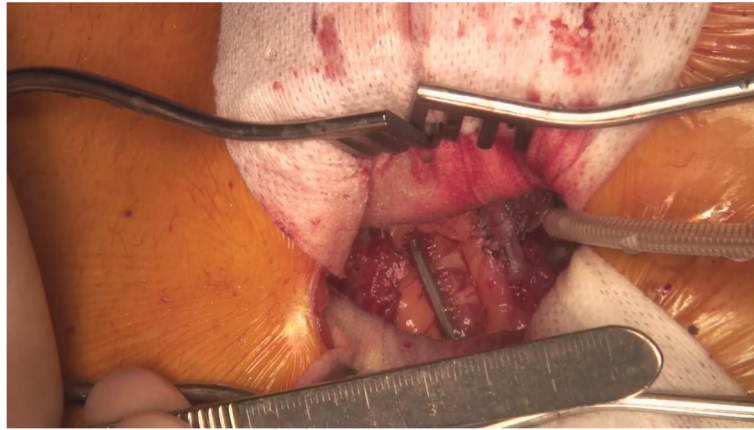
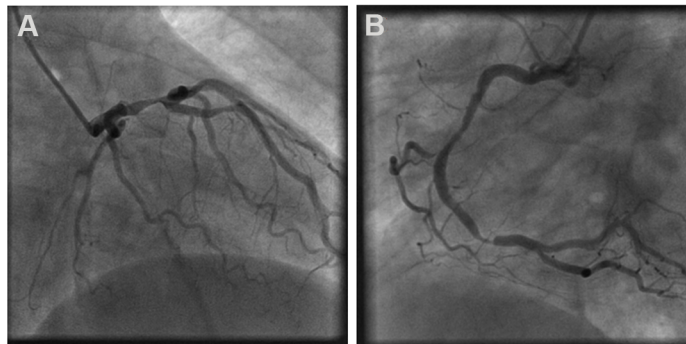


Figure 7. Robotic coronary artery bypass: stabilization and distal anastomosis.

Before



After

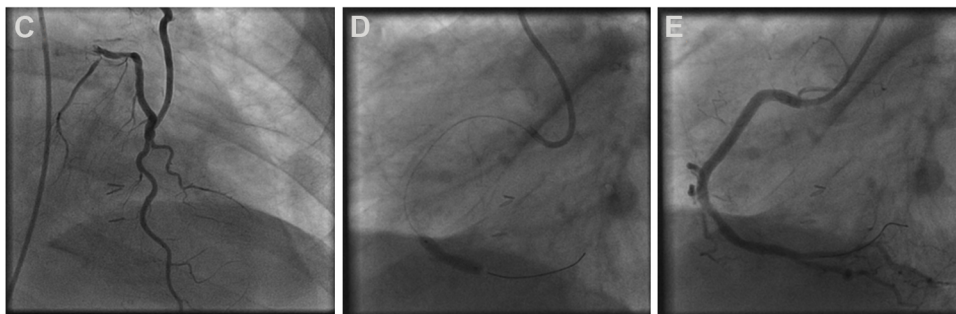


Figure 8. Hybrid coronary revascularization coronary angiogram: robotic left internal mammary artery to left anterior descending and stenting of the proximal circumflex artery.

HCR AND CARDIOPULMONARY BYPASS

Efforts to move towards a minimally invasive approach have been spearheaded by surgeons who developed expertise in OPCAB, interested in combining the benefits of minimally invasive approaches and OPCAB. Therefore, all of our robotic-assisted cases at Emory are performed off-pump for the LIMA LAD anastomosis, using specially designed, minimally invasive tissue stabilizers for robotic cases. In patients where we suspect we may need a cardiopulmonary bypass, the initial favored approach is a standard median sternotomy.

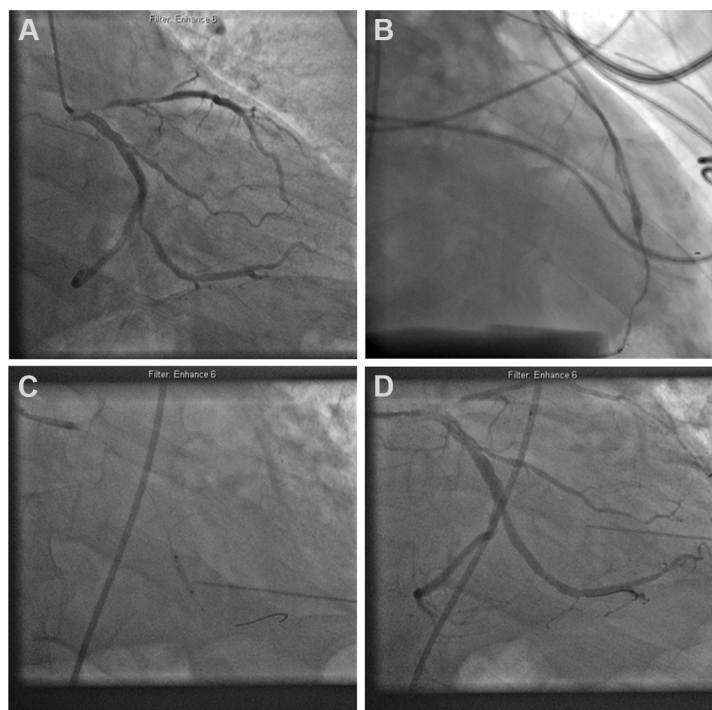


Figure 9. Hybrid coronary revascularization coronary angiogram: robotic left internal mammary artery to left anterior descending and stenting of the distal circumflex artery.

TIMING OF HCR STEPS

It is important to understand that HCR has two components: minimally invasive or robotic-assisted CABG and PCI. The sequence in which these two steps are performed matters and has clinical, scheduling, and even financial consequences. A comparative summary of the advantages and disadvantages of each sequence is presented in [Table 1](#).

Our preference at Emory is to perform the LIMA-LAD first when possible. In patients with stable coronary disease, this has several advantages, including the ability to perform the surgical procedure without concerns for dual antiplatelet therapy and interrogate the anastomosis angiographically during the subsequent cardiac catheterization. However, for patients that present to the hospital with an acute coronary syndrome, the general rule is to treat the culprit lesion first.

The LIMA LAD anastomosis can be done during the same admission or staged 1-2 months later if the LAD anatomy permits^[13,17]. The most convenient option for the patient is a concomitant procedure in a hybrid room where the PCI portion of the procedure can be performed immediately after the anastomosis.

The main advantage for the clinician is that graft patency can be confirmed immediately on the operating table, and any technical complications can be addressed while still in the operating room.

However, the logistical challenges of scheduling for both surgeons and interventionalists can make this difficult.

Table 1. Comparison of the three strategies available to perform the steps of HCR

Minimally invasive CABG first	Stent first	Same setting
Advantages		
Less risk of bleeding during the CABG	Bails out to conventional surgery if PCI unsuccessful without need for second surgery; helpful option for CTO PCI of non-LAD vessels	Convenient for patient
LIMA LAD provides protection during subsequent PCI	Allows immediate, expeditious coronary revascularization in patients presenting with acute coronary syndromes in non-LAD territories with lesions amenable to PCI	Lower total periprocedural length of stay
Able to study the LIMA LAD anastomosis at time of subsequent PCI		Most financially efficient
Disadvantages		
Incomplete revascularization during the higher cardiac demands of postoperative recovery	No LIMA LAD protection for multivessel PCI	Difficult coordination of multiple teams: scheduling is inefficient as one team has to wait for the other to finish and ties up operating room and cath lab personnel
Unsuccessful PCI requires a second surgery	Highest risk of bleeding during CABG due to need for dual antiplatelet therapy after stent (extended administration)	Slightly higher risk of bleeding due to loading dose of dual antiplatelet agents for PCI
Requires two separate procedures	Requires two separate procedures	Longest procedural duration

HCR: Hybrid coronary revascularization; CABG: coronary artery bypass; CTO: complete total occlusion; PCI: percutaneous coronary intervention; LAD: left anterior descending; LIMA: left internal mammary artery.

SELECTION OF PATIENTS FOR HCR AND PERFORMING HCR IN SPECIAL CIRCUMSTANCES

The ideal candidate for HCR

Experience has taught us that the best-suited patients for HCR are the ones with proximal, focal coronary lesions in fairly large coronary arteries that have a relatively low burden of calcium. Thus, the mid or mid to distal LAD is the prime target for a minimally invasive approach. On the other hand, an intramyocardial LAD is a relative contraindication for HCR because it is very difficult to identify and trace such a vessel through the limited exposure of small thoracotomy attention should be paid to examine the preoperative cardiac catheterization for straight segments of LAD, particularly ones that tend to move inward in systole more than the rest of the LAD, and particularly in the mid LAD.

Body habitus plays a significant role in the success of HCR. In the surgeon's early experience, the ideal patient should be tall, fairly thin, with large pleural cavities and a relatively small heart. A large heart can make harvesting the LIMA very difficult and increases the risk of either LIMA or cardiac injury. Early in our experience, we required two criteria for inclusion: one was a good LAD target vessel for bypass, and the second was a good body habitus for a minimally invasive left thoracotomy approach. We adhered strictly to this protocol for the first 200-300 cases, but currently, all we require is one of the above. [Table 2].

Table 2. Relative indications and contraindications of HCR

Relative indications	Relative contraindications
Low-intermediate SYNTAX score	High SYNTAX score
Proximal focal coronary lesions	Left thoracotomy, left lung surgery
Low burden of calcium in the coronary arteries	Home oxygen requirements
Good target vessels (large LAD)	Hemodynamic instability
Large pleural cavity	Preoperative need for intraaortic balloon pump
Small heart	Obese (particularly morbidly obese) patients
Thin, tall body habitus	Suspicion of intramyocardial LAD

SYNTAX score: angiographic grading system that evaluates the complexity of lesions in coronary artery disease, ranging from 0 (least complex) to 60 (most complex) and derived from the “SYNergy between percutaneous coronary intervention with TAXUS stent and cardiac surgery” trial.
HCR: Hybrid coronary revascularization.

HCR in patients with chronic obstructive pulmonary diseases

Chronic obstructive pulmonary diseases (COPD) poses an interesting challenge for the performance of HCR. On one hand, increased lung volumes increase left pleural cavity size and improve visualization and ability to harvest the mammary greatly. On the other hand, medium and small airway obstruction can trap air and make visualization difficult. Our preference is to use double-lumen tubes versus bronchial blockers in such patients as this allows better deflation of the left lung. The use of CO₂ insufflation for robotic cases can result in respiratory acidosis and hypotension much faster than in patients without COPD; the anticipation of these issues, administration of bronchodilators, and frequent blood gas checks.

With CO₂ insufflation, the other option is to use low tidal volume bilateral lung ventilation during the LIMA harvest and deflate the left lung during the anastomosis. Intermittent bilateral lung ventilation can also be used throughout the procedure. In general, we have found that almost all patients who are not on home supplemental oxygen are able to tolerate either single or low-tidal volume bilateral lung ventilation safely.

HCR in patients with chest wall deformities (prior trauma, chest wall radiation, kypho-scoliosis, pectus deformities)

Such patients can pose substantial challenges for minimally invasive CABG because of difficult visualization and possible unpredictable course or complete occlusion of the LIMA in case of prior trauma with rib fractures or radiation. Thus, again, the decision should be made on a case-by-case basis, taking into account the severity of the deformity, its particular location, the likelihood of direct interference with the operation, and most important the experience of the operator with minimally invasive CABG procedures.

HCR for left main disease

CABG is considered the standard of care for left main disease (LMD). Recently, however, after the results of the EXCEL trial, PCI has been upgraded as an acceptable alternative for LMD treatment. This has opened the possibility for HCR as a solution for LMD. However, performing a “limited intervention” in cases of LMD during the first step of the HCR can have adverse effects during the higher demands of postoperative recovery after a minimally invasive CABG procedure and until the patient can get completely revascularized with PCI. We compared 27 patients who had HCR with 81 contemporary patients treated with off-pump CABG for LMD. In all but one HCR patient, the left main was stented into the circumflex after LIMA LAD anastomosis. Immediate postoperative and medium-term outcomes were similar, except that the need for perioperative blood transfusions was significantly lower in the HCR group than the sternotomy CABG group. There was a trend towards a higher need for repeat revascularization at a median follow-up of 3.2 years, but not statistically significant - 2 patients in the HCR group vs. 1 patient in the CABG group,

$P = 0.9^{[13]}$. Certainly, this study was small but shows that such an approach is feasible.

In general, this option can be considered in patients with either distal left main bifurcation lesion or any lesion in the left main along with a proximal lad lesion. Isolated ostial or body lesions should not be considered for HCR b/c; there will be significant competitive flow with the LIMA b/c; there will no longer be a proximal lesion after PCI of the left main.

HCR for patients with a low ventricular ejection fraction

Poor contractility makes any cardiac intervention more difficult, and HCR is no exception. The challenge is augmented by the fact that the heart cannot be fully visualized during the CABG part of the operation. Nevertheless, such patients tend to tolerate poorly marginal oxygenation and ventilation that can occur with single lung ventilation. As a general rule, if cardiopulmonary bypass assistance may be needed, our preference is to perform median sternotomy.

HCR in patients with previous left lung surgery or who had previous left thoracotomies

In our experience, robotic HCR in those circumstances is generally contraindicated. The situation offers the challenge of creating an adequate working space to harvest the LIMA and perform the LIMA to LAD anastomosis because of previous adhesions. Equally challenging can be the fact that the heart can be displaced much further to the left, particularly after left lower lobectomies. It is paramount, particularly in situations of previous left anterolateral thoracotomies, to verify the patency of the LIMA at the time of preoperative cardiac catheterization, as it could have been injured and ligated during the previous surgery. Also, after left lung cancer surgery, it is possible that the patient had radiation to the chest wall on the left, and this can make harvesting the LIMA exceedingly difficult. For all these reasons, the patient might be better served with a conventional CABG and alternative arterial conduits, but these decisions should be made on a case-by-case basis with considerations for the risks and benefits of each approach.

SAFETY OF HCR

Quality of the LIMA conduit and LIMA LAD anastomosis

One of the most important questions about HCR concerns exactly that topic: given the different visualization during harvesting as well as limited exposure during the anastomosis, is this truly a comparable end product to the well-established gold standard results of median sternotomy LIMA to LAD operation? A comparison between our early HCR group versus median sternotomy off-pump CABG group indicates that issues with either the LIMA or the LIMA to LAD anastomosis are potentially more prevalent in the HCR group^[14]. However, these were rarely clinically driven ischemia events in the HCR group. In addition, almost all of the patients in the hybrid group underwent LIMA angiography, and almost none of the patients in the CABG group underwent postoperative angiography. Thus, the comparisons were not standardized, and minor defects early after anastomosis are more likely to be identified.

Our recommendation is to perform completion or postoperative angiography during the surgeon's early experience with robotic-assisted CABG for quality control purposes. This was our model for almost all of the first 3-400 cases. This provides opportunities for refinements in technique, ensures optimal quality outcomes, and ensures that excellent results are achieved with minimally invasive approaches. Our current patency rate approaches 98% for patients who underwent completion or postoperative catheterization.

One important question is what to do if a mild narrowing or physiologically insignificant defect is detected at or near the distal anastomosis when PCI is performed during the second stage of HCR. There is no compelling literature data about this issue. Certainly, an argument could be made about using invasive

functional evaluation (fractional flow reserve calculations - iFR/RFR); however, technical issues that can occur in attempts to cross a fresh anastomosis with a wire could be a problem. Our experience, which we are in the process of analyzing for mid and longer-term results, has been that the majority of these should not be intervened on early, particularly if there is TIMI 3 flow distal to the anastomosis. Instead, repeat angiography in 6-8 weeks, and possible iFR/RFR is recommended, and if necessary, intervention can then be performed.

Major adverse cardiac and cerebrovascular events (MACCE - death, myocardial infarction, and stroke)

In most published series, there are no statistically significant differences in hospital MACCE between the HCR group when compared to our conventional sternotomy patients^[14,18-22]. However, our current experience suggests a low risk-adjusted mortality rate < 1% and a stroke rate that is comparable to PCI at approximately 0.5%.

One important finding was that the incidence of perioperative myocardial infarction was not statistically different (0.7% vs. 0.5% in the HCR vs. the conventional group, $P = 0.8$)^[14]. This alleviates concerns that partial revascularization, either by single vessel CABG or PCI, during the initial part of the procedure would increase the risk of perioperative myocardial infarction due to increased risk of perioperative demand ischemia during the interim period between both procedures^[18-22].

In general, if patients present with an acute coronary syndrome secondary to a non-LAD culprit lesion, they should undergo PCI of the non-LAD culprit lesion first. If the LAD lesion is not critical, it can be staged 4-6 weeks later.

If the LAD lesion and the non-LAD lesion(s) are both critical, LIMA LAD grafting should be done first, and PCI should be done postoperatively during the same hospital stay. For non-critical lesions, the procedures can be staged over weeks.

The goals of HCR should be the same as for CABG and multivessel PCI - complete revascularization for all patients.

Risk of bleeding

An important question about HCR is the risk of bleeding due to the mandatory need for antiplatelet agents in the perioperative period. A pivotal role in the success of HCR is played by the use of DES. Such stents have a long-term patency rate comparable to vein grafts, and second-generation DES are less thrombogenic compared to bare metal stents; however, early thrombosis due to delayed endothelialization can still be an issue. Dual antiplatelet therapy is mandatory after DES, and the risk of stent thrombosis, with associated myocardial infarction or sudden death, doubles for the first generation stents if that therapy is stopped^[7,8,23]. Even with the second-generation DES, permanent discontinuation of dual antiplatelet therapy before thirty days from stent insertion results in a high risk of stent thrombosis (hazard ratio = 26.8, 95% confidence interval: 8.4-85.4, $P < 0.0001$); permanent discontinuation after 90 days does not seem to be associated with a higher risk of stent thrombosis^[23].

For patients that have undergone a PCI first strategy for HCR, we recommend the continuation of DAPT even for their surgery. Modifications of these recommendations will depend on guideline changes for the duration of DAPT for the latest generation of DES.

At Emory, we use a staged strategy preferentially, performing the robotic LIMA LAD first, then the PCI, unless the culprit vessel is a non-LAD vessel, in which case PCI is performed first. With this strategy, our blood transfusion requirements have been statistically significantly less in the HCR group than in the sternotomy CABG group (35.4% vs. 56%, $P < 0.001$)^[14]. Similar results have been confirmed by others^[17]. However, a larger study is necessary to elucidate this issue, as it is possible that performing PCI routinely first, before the portion of the procedure, can increase the risk of bleeding due to the more widespread use of dual antiplatelet therapy. Our current transfusion rate for HCR procedures is approximately 15% of patients undergoing robotic-assisted CABG, which is significantly less than sternotomy patients - 25%-30%.

A word of caution should also be said about the particular type of antiplatelet agents used: most of the studies have been done with the combination of Aspirin and Plavix (Clopidogrel). Newer agents like Brilinta (Ticagrelor) or Effient (Prasugrel) have not been studied extensively in this setting, and it is possible, particularly if PCI is done first and particularly if Effient (which is much more potent at platelet inhibition) is used, that the bleeding complications will be higher in the HCR group.

For patients on these newer generation antiplatelet agents, we usually transition them to clopidogrel if they are sensitive to this agent 7 days before surgery to avoid performing surgery on ticagrelor or prasugrel.

Mistaking a diagonal branch for the LAD

Mistaking a diagonal branch for the LAD can occur at times, particularly if the LAD is small, intramyocardial or the target LAD lesion is very distal, as mentioned above. If there is no stenosis between the ostium of the diagonal and the LAD, grafting a LIMA to diagonal instead of the LAD has two main drawbacks: the diagonals are much smaller vessels, and the diagonals lack septal perforators, which reduces the vascular bed available for immediate perfusion substantially. Both of these factors can result in decrease patency rates for the LIMA and inadequate long-term flow in the anterior region of the heart.

For these reasons, if the mistake is recognized intraoperatively, we recommend transecting the LIMA as close as possible to the diagonal anastomosis after applying a small clip on the LIMA flush with the diagonal and re-grafting the LAD with the LIMA. If this complication is recognized during the index procedure, it almost always can be addressed during the same setting by dividing the LIMA at the diagonal anastomosis and grafting it onto the LAD.

ADVANTAGES OF HCR: WHAT HCR CAN DO WELL AND WHAT IT DOES ONLY MARGINALLY BETTER THAN CONVENTIONAL CABG

The main advantages to a hybrid approach are the following:

- (1) The major benefit of CABG is still achieved with LIMA LAD grafting;
- (2) There is a lower transfusion rate^[14,17] compared to conventional CABG;
- (3) Risk of stroke is lower because there is no aortic manipulation and no cardiopulmonary bypass;
- (4) The risk of serious wound complications (mediastinitis) is avoided;
- (5) Return to normal activity and recovery time are much quicker;
- (6) Improved cosmesis.

The main goal with HCR is for patients with proximal LAD disease who may have otherwise been treated with PCI to the LAD can derive the long-lasting benefits associated with LIMA LAD grafting. In addition, most of the patients that undergo robotic-assisted CABG would have otherwise been treated with multivessel PCI, not CABG.

DEVELOPING A SUCCESSFUL HCR PROGRAM

The prerequisite for a surgeon to start a successful HCR program is to master the techniques of at least one minimally invasive CABG approach and off-pump coronary bypass. These two goals are difficult to be tackled simultaneously. Off-pump LIMA LAD grafting is best mastered in open sternotomy cases under the careful supervision of a seasoned mentor. However, the pathway for training could be different for a young surgeon just out of training vs. an experienced surgeon routinely performing the on-pump, arrested technique. Training in a program experienced with off-pump and beating heart surgeries in its different varieties or joining a group with extensive expertise in such techniques would be the best path forward for the young surgeon. The surgeon will be coached to avoid serious mistakes and gain the expertise and confidence to become a skilled surgeon. These skills can then be translated into a minimally invasive platform.

For the seasoned surgeon with expertise in on-pump arrested CABG, a short period of observation in a busy off-pump program, followed by the transition to performing LIMA to LAD anastomosis on a beating heart, but in a pump assisted fashion, followed by the performance of LIMA to LAD completely off-pump in conjunction with conventional on-pump, arrested technique for the other anastomoses, would lead to expertise during one's own practice.

The harvesting of the mammary artery can be learned as a second step or simultaneously. A minithoracotomy approach harvest is probably the easiest to learn in a self-taught manner after observing cases and watching videos. However, due to the complexities of positioning the robot, training a whole team, and actually learning the technique, robotic cases are a much more ambitious goal and would require either a mini-fellowship or be reserved as a later goal.

First of all, the exposure, be it mini-thoracotomy or a 2-inch, the non-rib spreading incision used for robotic cases, offers a very different view of the heart than a surgeon is used to traditionally. This translates into difficulties in identifying the LAD target.

From the minimally invasive view, the LAD is the furthest vessel to the right; problems can appear, however, when the LAD is buried in epicardial fat or is intramyocardial. Therefore, it is paramount to make sure that the vessel furthest to the right on the anterior aspect of the heart has a general direction tracking to the apex of the heart. This can be verified by direct inspection through a minithoracotomy approach or by camera inspection with the robot and marking the vessel with a marking pen or clip after opening the pericardium robotically prior to performing the small access incision for the LIMA to LAD anastomosis.

CONCLUSION

In conclusion, HCR is a novel technique that can offer the next level of care for appropriately selected patients in the hands of expert surgeons, combining the benefit of long-term results offered by sternotomy CABG with rapid, short-term recovery and minimal morbidity. Such an approach is feasible if time and energy are invested in the training and logistical development of a collaborative approach.

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Authors' contributions

Conception, design and editing of the article: Pusca SV, Halkos ME

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Consent for publication

Consent for photography is obtained routine for every patient operated at Emory Healthcare Hospitals.

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Perspective

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Minimally invasive liver resection in Japan: is the robot necessary?

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Abstract

Robot-assisted hepatectomy (RAH) is rarely indicated in Japan because of the lack of reimbursement from the national health insurance system. Instead, laparoscopic hepatectomy has been approved for all hepatectomy procedures except resections requiring biliary reconstruction. An obvious advantage of RAH over laparoscopic hepatectomy is the fact that surgeons can use multi-articulated surgical devices, which may facilitate resection of superior/posterior hepatic regions, hilar dissection, biliary reconstruction, and hepatic segmentation by fluorescence imaging. With the accumulation of evidence supporting the use of robotic surgical devices in particular situations of hepatectomy, RAH will become more commonly indicated in Japan under the existing nationwide reporting system and board certification systems to assure surgical safety.

Keywords: Robot-assisted hepatectomy, laparoscopic hepatectomy, minimally invasive hepatectomy, anatomic hepatectomy, fluorescence imaging

INTRODUCTION

During the past three decades, the indications for laparoscopic hepatectomy (LH) have been dramatically extended based on technical, oncological, and regional factors. In Japan, LH for limited resections and left lateral sectionectomy was first reimbursed by the national health insurance system in 2010; this was



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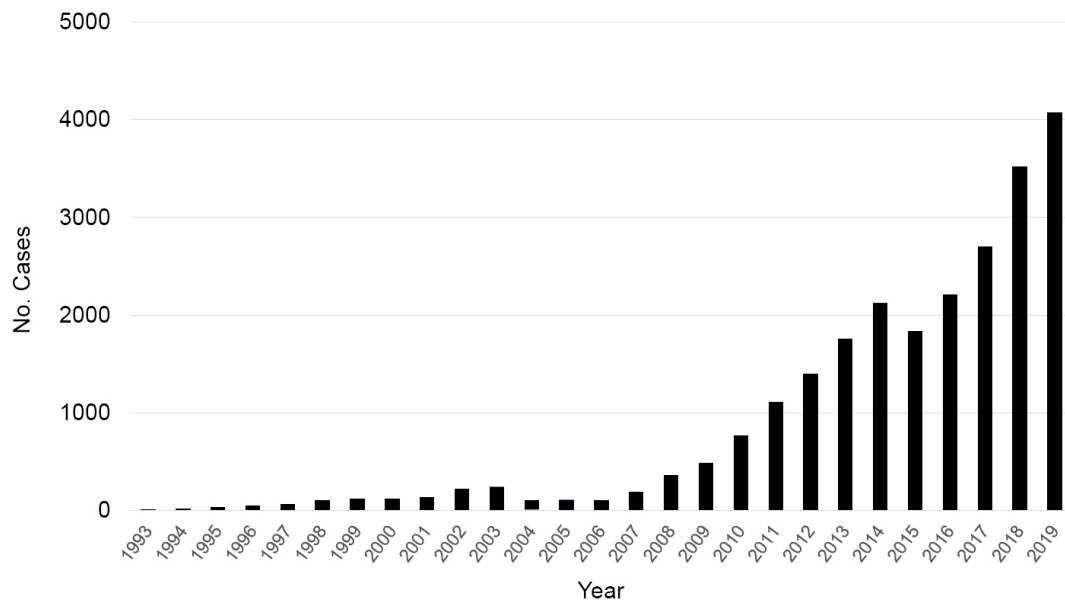


Figure 1. Trends of annual numbers of laparoscopic hepatectomies in Japan (1993-2019). Since the first insurance reimbursement in 2010, the numbers of laparoscopic hepatectomies have progressively increased, and this increase has been further boosted by the extension of insurance support to a wider range of hepatectomy procedures in 2016. This figure was created based on the 15th Nationwide Survey of Endoscopic Surgery.

followed by extension of its indications to all LH procedures except hepatectomy requiring biliary reconstruction in 2016^[1] and reimbursement of robot-assisted distal pancreatectomy and pancreaticoduodenectomy in 2020. As of 2021, however, robot-assisted hepatectomy (RAH) has not been reimbursed. We herein introduce the current status of minimally invasive hepatectomy in Japan and discuss the potential advantages of RAH over conventional hepatectomy procedures in an effort to promote future proliferation of robot-assisted hepatobiliary surgery.

CURRENT DISSEMINATION STATUS OF RAH IN JAPAN

Since the first insurance reimbursement in 2010, the number of LH cases in Japan has progressively increased, and this increase was further boosted by the extension of insurance support to a wider range of hepatectomy procedures in 2016 [Figure 1]. Based on the National Clinical Database, 13% of hepatectomy procedures (more than one segment excluding the lateral segment) were performed laparoscopically in 2019^[2]. In contrast, RAH has rarely been performed in Japan; according to the 15th Nationwide Survey of Endoscopic Surgery, RAH accounted for only 0.5% of all minimally invasive hepatectomy procedures performed in 459 medical centers belonging to the Japan Society for Endoscopic Surgery [Table 1, The 15th Nationwide Survey of Endoscopic Surgery in Japan (The Japanese Society for Endoscopic Surgery)]. In Japan, where all citizens receive medical care under the universal health insurance system, insurance reimbursement is critical for both patients and surgeons to ensure access to newly developed therapeutic modalities such as robot-assisted surgery.

Another feature to consider in the dissemination of RAH is the safety of hepatectomy in Japan. Even after the nationwide establishment of LH, the overall mortality rates after hepatectomy remained quite low (0.7%-1.4% at 30 days and 1.3%-2.6% at 90 days from 2011 to 2019), with favorable morbidity rates (3.4%-4.3% Clavien-Dindo grade IIIa-V complications)^[2]. Step-by-step establishment of LH under the board certification systems provided by the Japan Society for Endoscopic Surgery^[3], the Japanese Society of

Table 1. Numbers of different minimally invasive hepatectomy procedures in Japan in 2019*

	Pure LH	RAH	Others [†]
Wedge resection	2663	9	131
Couinaud's segmentectomy	348	2	9
Left lateral sectionectomy	275	1	14
Sectionectomy	311	2	17
Bisectionectomy	260	5	15
Trisectionectomy	10	0	1
Total	3867 (94.9%)	19 (0.5%)	187 (4.6%)

*Based on the 15th Nationwide Survey of Endoscopic Surgery in Japan (the Japan Society for Endoscopic Surgery). [†]Hand-assisted or hybrid procedures. LH: Laparoscopic hepatectomy; RAH: robot-assisted hepatectomy.

Hepato-Biliary-Pancreatic Surgery^[4,5], and the nationwide online registry system^[6] have contributed to the safe and consistent dissemination of LH in Japan.

POSSIBLE ADVANTAGES OF PROMOTING FUTURE DISSEMINATION OF RAH

Recent systemic reviews and meta-analyses have already shown that RAH offers acceptable operative outcomes at least comparable to those of LH, except for possible extension of the operation time^[7-9]. More recently, a meta-analysis focusing on major (three or more Couinaud's segments) hepatectomies suggested advantages of RAH over LH in decreasing a conversion rate and perioperative blood loss^[10]. Considering the higher cost of RAH^[7,9], however, we need more evidence supporting the clear advantages of using robotic surgical systems in specific aspects of hepatectomy procedures, as suggested below, which enables selection of the patient appropriate to RAH.

Resection of superior/posterior hepatic regions

One of the major limitations of LH lies in the fact that conventional procedures allow only tangential movements of laparoscopic forceps. This makes deep wedge resections difficult to perform, especially for lesions located in the right superior/posterior regions of the liver. Using a "lateral approach" with intercostal trocars^[11,12] is a possible solution for LH, but this technique may not be applicable to patients with a history of pulmonary disease or surgery. Vertical transection of the hepatic parenchyma enabled by multi-articulated movements of robotic devices may facilitate resection of hepatic tumors located in difficult regions, as suggested by a previous comparative study^[13]. Melstrom *et al.*^[14] also suggested efficacy of RAH in decreasing postoperative hospital stay (even on the day of surgery), especially in cases of superior/posterior hepatic regions where the incision for open surgery would dominate the course of recovery.

Hilar dissection and biliary reconstruction

Flexible movements of robotic surgical forceps also enable minute dissections of hepatic vessels running in the hilar plates and hepatoduodenal ligament; this may be associated with favorable operative outcomes with a lower probability of open conversion in major hepatectomies and complicated hepatectomy procedures requiring hilar dissection as compared with LH^[7,10,15]. Suturing with the use of multi-articulated needle holders is an obvious advantage of robot-assisted surgery over conventional laparoscopic techniques. In the context of hepatobiliary surgery, this feature would work most effectively for biliary anastomosis as demonstrated in surgery for choledochal cysts^[16], although no LH procedures requiring biliary reconstruction have been reimbursed by the Japanese health insurance system to date.

Hepatic segmentation by fluorescence imaging for anatomic resection

Because the latest robotic surgical systems are equipped with near-infrared imaging technology (da Vinci Firefly; Intuitive Surgical, Sunnyvale, CA, USA), intraoperative fluorescence imaging using indocyanine green (ICG) can be easily applied to RAH as well as LH and open hepatectomy for real-time visualization of the biliary anatomy (fluorescence cholangiography), liver cancers, and boundaries of hepatic segments^[17]. Among these procedures, hepatic segmentation can be achieved by direct injection of ICG into the target portal branch (positive staining technique)^[18,19] or by systemic injection of ICG following closure of the portal pedicle feeding tumor-bearing hepatic segments (negative staining technique)^[18,20]. If a robotic surgical system could be used to perform a positive staining technique, it would facilitate easier puncture of the target portal branch under ultrasound guidance compared with laparoscopic needle manipulation^[21]. The use of robotic surgical devices also enables multidirectional dissection of the hepatic hilum to reach the corresponding Glissonian sheaths to be divided^[22], which may extend the indications for the negative staining technique to anatomic resection of deeply located hepatic segments. Although near-infrared imaging has been installed in the latest model of laparoscopic imaging systems as well as robotic surgical systems, use of this technology with multi-articulated forceps and three-dimensional color imaging may further extend applications of fluorescence imaging during hepatobiliary surgery.

Integrated surgical navigation, autonomous actions, and surgical decision-making by artificial intelligence

In addition to intraoperative information obtained by techniques such as fluorescence imaging and ultrasonography, preoperative simulation can be placed in the surgeon's console of the robotic surgical system and displayed in real time with three-dimensional images of operative fields. In this respect, RAH has a potential advantage over LH in terms of the ability of surgeons to understand special relationships between anatomical structures and tumors by integrating preoperative and intraoperative imaging information. Applications of augmented reality^[23] and artificial intelligence^[24] may further promote the development of surgical navigation systems. In addition, application of artificial intelligence in robotic surgery may enable autonomous control of surgical installments like a laparoscope and staplers and provide precision information for accurate surgical decision-making^[25].

POSSIBLE DISADVANTAGES OF APPLYING ROBOT-ASSISTED SURGERY TO HEPATECTOMY

As mentioned previously, the major disadvantage of RAH over LH is the higher cost associated with the initial installation and use of each instalment. Especially in Japan, the amount of future insurance claim for RAH may be the same as that for LH as in the case of pancreatectomy, which can press management of the medical institutions. Limited lineup of aspiration and dissection devices (no angular ultrasonic dissectors) designed for hepatic parenchymal transection is another drawback of RAH, leading to longer operation time than LH as demonstrated in previous studies^[7-9]. We expect that the next-generation robotic surgical systems are devised with the opinions from liver surgeons to adjust to the specific conditions of hepatectomy.

CONCLUSIONS

With the accumulation of evidence indicating the specific advantages of RAH over LH, robotic surgical systems will become more commonly used for hepatobiliary surgery in Japan as well as in other countries. After reimbursement by the health insurance system, we aim to apply RAH with prioritization of surgical safety using a nationwide reporting system and board certification systems for the performance of LH and robot-assisted pancreatic resections.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the study, performed the data analysis and interpretation, and wrote the manuscript: Ishizawa T

Provided administrative and technical support and critical revisions of the manuscript: Hasegawa K

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Review

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Left atrial appendage occlusion in patients with atrial fibrillation: focus on current evidence and commercially available devices

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Abstract

Atrial fibrillation is the most common cardiac arrhythmia and is associated with morbidity and mortality due to cerebral or systemic embolization, with cardiac thrombi mainly forming in the left atrial appendage (LAA). Anticoagulation is the treatment of choice; however, in patients who do not tolerate anticoagulation, LAA occlusion (LAAO) is a valid alternative. Over the last decade, many different LAAO devices have been developed and tested in trials, providing good clinical results. The purpose of this paper is to make an overview of the current state of the art of LAAO procedure, with a focus on available devices and future perspectives.

Keywords: Left atrial appendage, left atrial appendage occlusion, atrial fibrillation, stroke prevention

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with cerebral or systemic embolization as a result of possible thrombus formation in the left atrium and left atrial appendage (LAA)^[1]. In addition, AF is associated with increased mortality^[2].



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Anticoagulation has been shown to reduce the risk of embolization in AF^[3,4]. However, in patients with high bleeding risk who are not candidates for anticoagulation, a different approach should be evaluated. Due to its anatomical characteristics and low-flow state predisposing to blood stasis and thrombosis, most atrial thrombi form in the LAA^[5]. For this reason, percutaneous and surgical techniques have been developed over the years to exclude the LAA and prevent systemic embolization in AF. The purpose of this paper is to make an overview of the current state of LAAO procedure, with a focus on available devices and future perspectives.

ASSESSING THE BLEEDING AND STROKE RISK IN AF

The most feared complication of AF is systemic embolism, with ischemic stroke being the most clinically relevant and catastrophic event. While anticoagulant therapy is effective in reducing embolization, bleeding risk may equal or exceed embolic risk without anticoagulation in some patients^[6].

Therefore, clinicians are used to estimate ischemic and bleeding risk with different scores that are useful to choose the adequate management strategy. The CHA₂DS₂-VASc^[7] and HAS-BLED^[8] scores provide an estimate of the risk of stroke and bleeding events, respectively. Current guidelines (both European and American)^[9-11] do not recommend antithrombotic treatment in patients with a CHA₂DS₂-VASc score = 0 in males and = 1 in females, while anticoagulation is indicated for higher scores. Regarding bleeding risk, modifiable risk factors in high-risk patients (HAS-BLED ≥ 3) should be addressed and flagged up for regular follow-up with close INR monitoring or adjustment of the dose of anticoagulant medications, when possible. Of note, high scores should not be used as a reason to withhold oral anticoagulation (OAC) if a patient is considered eligible.

INDICATION FOR LAAO

For AF patients at high risk for ischemic stroke (CHA₂DS₂-VASc score ≥ 1 in males and ≥ 2 in females) who should receive anticoagulation but for whom OAC is contraindicated, both European and American guidelines give a IIb class recommendation for percutaneous LAAO to prevent systemic embolism^[9,11]. Patients with the following characteristics may be included in this category:









- Prior severe bleeding (e.g., intracranial hemorrhage without a reversible cause).
- Diagnosed coagulation defect related to hemorrhage.
- History of recurrent bleedings (e.g., genitourinary or gastrointestinal) and anemia.
- Poor compliance or intolerance to OAC.

Furthermore, LAAO may also have a role in patients who refuse antithrombotic therapy due to personal preferences. While this population has not yet been extensively studied, future trials will focus on these patients, and indications for LAAO may considerably enlarge.

Currently available devices

Percutaneous LAAO devices are based on three different principles: the plug, the pacifier, and the ligation^[12]. While many different percutaneous devices are available in Europe, only two of them are currently FDA approved. In addition, surgical LAA exclusion can be performed via thoracoscopy with the AtriClip (FDA approved in 2010). The main characteristics of the current devices are summarized in [Table 1](#).

Table 1. Available left atrial appendage occlusion devices. Adapted and modified from the 2020 EHRA/EAPCI expert consensus statement update on catheter-based left atrial appendage occlusion^[12]

Device name	Manufacturer	Principle	RCTs	Advantages	Potential disadvantages	Image
WATCHMAN	Boston Scientific	Plug	PROTECT-AF ^[13] , PREVAIL ^[14]	Strong scientific evidence supporting its use (2 RCTs). Large clinical experience due to widespread use	May not be suitable for very short appendages due to its design	
WATCHMAN FLX	Boston Scientific	Plug	None	Second iteration of WATCHMAN device. It fits in less deep appendages and can be released more proximally	Relatively large (14 French) delivery system	
WaveCrest	Biosense Webster	Plug	None	Can be used in short appendages	Little experience about its use	
Amplatzer Cardiac Plug	Abbott Vascular	Pacifier	None	Large registries documenting its use. Can be used in short appendages (it is shorter than the WATCHMAN)	First generation device. Less stable and higher rate of incomplete closures than Amulet	
Amulet	Abbott Vascular	Pacifier	AMULET-IDE ^[15]	Large registries and 1 RCT about its use. More stable and larger lobe than the ACP. Good for short LAAs (it is shorter than WATCHMAN). Large clinical experience	May not be the device of choice in very deep appendages due to its design (larger than deep). Relatively large (14 French) delivery system	
Ultraseal	Cardia Inc.	Pacifier	None	Disc and lobe are connected by a flexible joint allowing orientation of the disc even in tortuous LAAs	Sealing depends mostly on disc. Little experience about its use	
Lambre	Lifetech	Pacifier	None	Can be implanted in very different LAA anatomies	Sealing depends mostly on disc. Little experience about its use	
ATRICLIP	AtriCure	Surgical epicardial exclusion	None	No foreign material in contact with blood. Allows complete LAA occlusion	Requires thoracoscopic access	

ACP: Amplatzer cardiac plug; RCT: randomized clinical trial; LAA: left atrial appendage.

The plug principle

Plugs are endovascular-delivered devices consisting of a lobe or umbrella that obstructs the neck of the LAA excluding it from the atrial cavity when it is completely endothelialized. The first CE-approved (CE-mark in 2005) device exploiting this principle is the WATCHMAN™ (Boston Scientific Corporation,

Marlborough, MA). This device consists of a self-expandable nitinol cage covered by a membrane of polyethylene terephthalate (PTFE) [Figure 1] which is fully endothelialized by the heart tissue, resulting in permanent LAA sealing. The implant procedure is performed via the femoral vein with transesophageal echocardiography (TEE) or intracardiac echocardiography guidance, and its deployment requires a transseptal approach [Figure 1C]. The second iteration of this device, WATCHMAN FLX, has been available since 2019 and may overcome some limitations of the first-generation occluders, with its higher suitability for shallower anatomies.

As of today, this device is the only LAAO device that has been prospectively compared with warfarin in two randomized controlled trials (PROTECT-AF and PREVAIL^[13,14]) of AF patients without contraindication to OAC. The antithrombotic protocol of these studies consisted of a post-procedural 45-day period of warfarin anticoagulation, followed by a 6-month DAPT (aspirin and clopidogrel), which was followed by SAPT therapy (aspirin) indefinitely. Five-year outcomes of these two trials demonstrated that LAA occlusion provides stroke prevention in nonvalvular AF comparable to warfarin, with significant reductions in major bleedings and all-cause mortality (HR = 0.48; $P = 0.0003$ and HR = 0.73; $P = 0.035$, respectively)^[16]. Furthermore, the ASAP study showed that LAAO with the WATCHMAN™ can be performed even in individuals with an absolute contraindication to OAC^[17]. Given the solid scientific evidence, the WATCHMAN™ is a widely used device in daily clinical practice, and it was the first percutaneous device approved for LAA occlusion in the United States (FDA approval in 2015).

The principle of the plug is also exploited by the WaveCrest® (Biosense Webster, Irvine, CA), which obtained the CE mark in 2013 but is not FDA approved. This device may be useful in very short appendages as it is deployed more proximal, but it is less commonly used. A prospective, multicenter, randomized trial (NCT03302494) comparing this device and the WATCHMAN™ is currently recruiting patients in the United States.

The pacifier principle

The “pacifier-like devices” are inspired by patent foramen ovale and atrial septal defect occluders, consisting of a lobe that is delivered into the LAA with an additional disc to seal the LAA ostium. As for the plug system, LAA exclusion relies on endothelialization of the device. The most widely used device is the Amplatzer™ (Abbott Vascular, Chicago, IL; CE-approved in 2013). Although no randomized trial against anticoagulation has been conducted, both the first (Amplatzer Cardiac Plug) and the second (Amulet) generation of this device have shown their efficacy in reducing the risk of ischemic stroke and major bleeding compared to the predicted risk^[18,19]. Compared to the Amplatzer Cardiac Plug, the newest Amulet has a deeper distal lobe with a more overriding proximal disc resulting in more complete LAA exclusion, especially for deeper LAAs [Figure 2A and B]. The recently published Amulet-IDE trial confirmed this finding, showing a higher LAA occlusion rate for the Amulet occluder compared with the WATCHMAN (98.9% vs. 96.8%; difference = 2.03%; 95% confidence interval (CI): 0.41-3.66; $P < 0.001$ for noninferiority; $P = 0.003$ for superiority)^[15]. As for the WATCHMAN™, Amulet deployment requires a transseptal approach during echocardiographic guidance. In August 2021, following the results of the Amulet-IDE trial, the Amplatzer™ Amulet received FDA approval, becoming the second percutaneous LAAO device available in the United States.

Other Pacifiers are the LAMBRE™ (Lifetech, China) and the Cardia Ultraseal™ (Cardia Inc., St Paul, MN). The former consists of a fabric-enriched cover and an umbrella connected with a central waist^[20], while the Ultraseal™ is composed of a distal anchoring bulb and a proximal sail connected with an articulating joint that allows multidirectional movements and adjustments to different LAA shapes and ostium angles^[21]. The

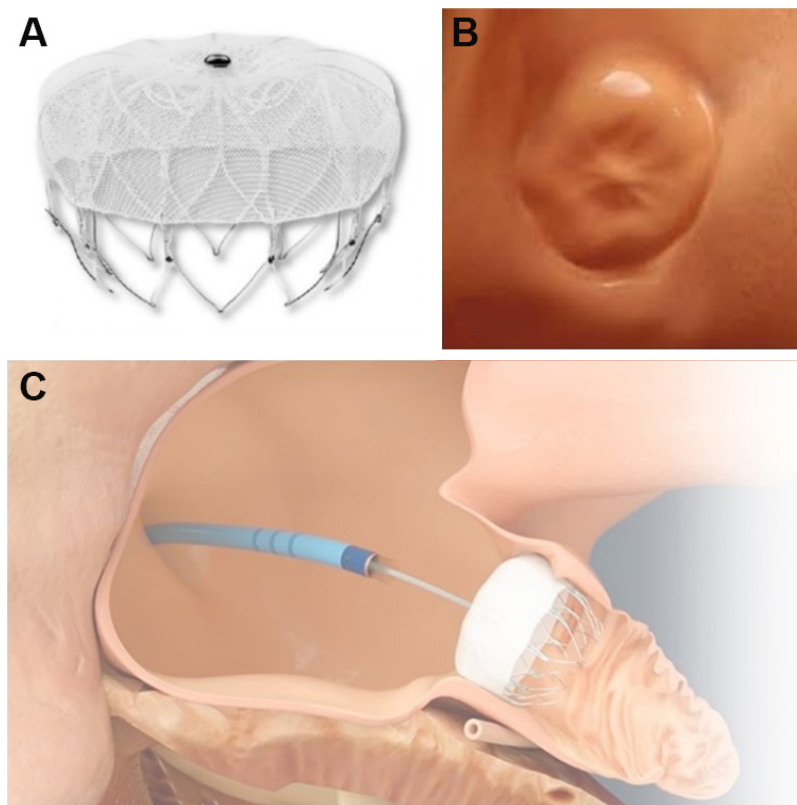


Figure 1. (A) The WATCHMAN and WATCHMAN FLX devices consist of a self-expandable nitinol cage covered by a membrane of polyethylene terephthalate (PTFE). (B) Heart tissue grows over the PTFE membrane guaranteeing device endothelialization and left atrial appendage (LAA) sealing. (C) The interatrial septum is crossed, and the device is released in the LAA.

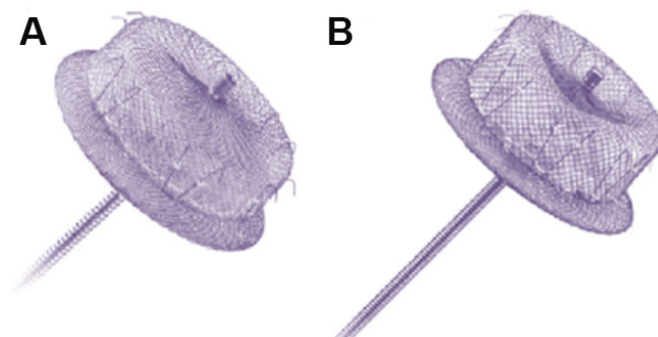


Figure 2. (A) First generation Amplatzer Cardiac Plug; and (B) second generation Amulet showing a deeper distal lobe with a larger proximal closure disc.

main advantage of these devices is that they possibly allow a complete closure of tortuous LAAs and of multilobulated appendages^[22]. Although both devices received the CE mark in 2016, they are still not widely used in clinical practice^[23].

The ligation principle

LAA ligation simulates surgical closure and consists of snaring and ligating the body of the LAA with a double epicardial and endocardial approach. This principle is exploited by the LARIAT™ (SentreHEART, Pleasanton, CA; CE approved in 2015), which is a suture delivery device that is released around the LAA

after both the epicardial and endocardial magnet-tipped guidewires have been connected together^[24]. After initial encouraging results^[24], subsequent multicenter studies reported high periprocedural complications with high rates of serious pericardial effusions^[25,26], which led the FDA to announce safety issues in 2015. For this reason, the use of the LARIAT™ has been significantly reduced and this device is actually limited to rare cases of difficult anatomies, unsuitable for fully endovascular closure. Interestingly, every device, except the LARIAT™, is made of nitinol, a mixture of nickel and titanium; therefore, device selection in patients severely allergic to nickel (e.g., extensive cutaneous reactions) is limited to the infrequently used ligation system, if deemed suitable by the operator.

Thoroscopic surgical closure

A special consideration has to be made for epicardial LAA occlusion. As many patients develop recurrent AF after catheter ablation, may be unsuitable for the percutaneous procedure, or prefer a more durable intervention, thoroscopic surgical AF ablation may be a valid alternative in patients with refractory and symptomatic AF^[27]. In these cases, since LAA electrical isolation creates an akinetic and highly thrombogenic cul-de-sac^[28], concomitant thoroscopic LAA clip closure may be indicated. The AtriClip® (AtriCure, Inc. West Chester, PA, USA) is an FDA-approved device for epicardial LAA management. This device, consisting of a preloaded nitinol cap, is placed at the level of the epicardium at the base of the LAA, resulting in a complete LAA exclusion^[28]. It has proven to reduce the incidence of stroke in AF patients undergoing heart surgery^[29]. Moreover, the recent LAAOS III trial, which randomized AF patients undergoing cardiac surgery to concomitant LAA closure (some of which with AtriClip®) or no closure, demonstrated a relative stroke risk reduction of 33% at 3.8 years, suggesting the potential benefit of this procedure^[30]. However, up to date, these results can be applied only to AF patients undergoing cardiac surgery, while the potential benefit of this procedure in patients undergoing thoroscopic AF ablation remains hypothetical, requiring further dedicated research.

LAA imaging

Before proceeding with LAA occlusion, imaging is fundamental to assess LAA anatomy and plan the procedure strategy. The main aspects to evaluate are the absence of LAA thrombosis and the LAA shape and size, to check for device compatibility. TEE and computed tomography angiography (CCTA) are the exams of choice. Even if CCTA may achieve high positive and negative predictive values and specificity, TEE is generally considered the gold standard in ruling out LAA thrombosis.

Thrombosis is visually confirmed with a careful evaluation of LAA body through different imaging planes, while LAA emptying velocity evaluation provides additional data about blood stasis. Low peak LAA emptying velocity (< 40 cm/s), in fact, may indicate a pro-thrombotic state and is a strong predictor of thrombus formation^[31]. Moreover, TEE with 3D acquisitions plays a fundamental role in evaluating LAA anatomy and device compatibility, as it allows carefully analyzing the LAA without intravenous contrast-medium injection. Good quality 3D images (preferably at high framerate with multi-beat acquisition) may be post-processed to evaluate LAA depth, width, morphology, and orifice diameters. Furthermore, TEE images are useful to choose the most suitable occluder type, with specific measurements guiding the selection of the correct device size. In particular, the Amulet's size is determined measuring the LAA orifice and the device landing zone (10-12 mm inside the orifice) at different angles, while WATCHMAN requires measurements of the orifice diameter and LAA depth.

As mentioned above, CCTA with 3D multiplanar acquisitions is a valid alternative to TEE in preprocedural planning as it allows evaluating the LAA anatomy and provides a high level of device selection accuracy^[32]. A small study even showed that LAA ostial perimeter measured on CCTA, compared to LAA TEE diameter, was associated with better prediction of the optimal device size^[33]. However, it is less specific than

TEE in detecting LAA thrombosis and can lead to misdiagnosis in the case of a “pseudo-thrombus” due to a delayed contrast flow into the LAA body. Moreover, it requires intravenous injection of nephrotoxic contrast medium.

Finally, image fusion is a very innovative technique that has gained popularity over the last years as an alternative to traditional imaging in guiding LAA occlusion procedures. This technology integrates the fluoroscopy into 3D CCTA and provides both real-time images regarding trans-septal puncture and device deployment and spatial information about the surrounding structures, which are difficult to assess with the 3D TEE alone. This technique, when performed by highly experienced operators, has been demonstrated to be even superior to standard TEE in terms of one-time successful deployment rate^[34]. However, due to the higher cost compared to standard imaging, we believe that it could enter common clinical practice only in high-volume centers where LAAO is routinely performed.

PERIPROCEDURAL COMPLICATIONS

The most relevant and frequent periprocedural complications of LAAO are pericardial effusion and device embolization, while others such as stroke or access-site-related complications are relatively rare.

Pericardial effusion may be completely asymptomatic, or it may present as acute/subacute cardiac tamponade. It may be related to the transeptal puncture or the manipulation of catheters and the device against the thin-walled left atrium. Incidence of serious pericardial effusion ranges from 2.2% to 5%, and pericardiocentesis has shown to be a safe and effective treatment for it^[35]. It should be performed immediately in the case of hemodynamic instability, while, in the case of subacute or mild effusion, non-steroidal anti-inflammatory drugs (e.g., aminosalicylic acid or ibuprofen) are the treatment of choice.

Device embolization may happen early, during the procedure, or later, during follow-up. Embolization occurs in < 0.5% of patients^[13]. Careful selection of the appropriate device and a correct deployment technique are the best way to avoid it. Percutaneous retrieval of the embolized device is the treatment of choice, if technically feasible, otherwise surgical retrieval may be required.

MANAGEMENT OF ANTITHROMBOTIC THERAPY

Periprocedural antithrombotic therapy

LAA closure is a percutaneous procedure, performed via transfemoral venous access. Anticoagulation with unfractionated heparin (UFH) is recommended during the procedure: it should be started prior to or immediately after transeptal puncture, at a dose of 70-100 IU/kg, aiming for an activated clotting time of \geq 250 ms. In patients with a contraindication to UFH, bivalirudin may be considered. Ideally, naive patients should receive a loading dose of acetylsalicylic acid (300-500 mg). Moreover, patients who are candidate to be discharged without oral anticoagulant therapy should be given an oral loading dose of clopidogrel (300-600 mg) prior to the procedure^[12].

Antithrombotic therapy discharge

The only available randomized clinical trials (RCTs) (PREVAIL and PROTECT-AF) did not include patients with contraindication to OAC. For this reason, the post-procedural management pursued in these studies consisted in a combination of warfarin (target INR 2-3) and aspirin 100 mg for the first 45 days, followed by a first six-month DAPT period (aspirin and clopidogrel) and then by SAPT indefinitely. However, most patients undergoing percutaneous LAA closure have an absolute contraindication to OAC. In these cases, as endorsed by the recent EHRA/EACPI expert consensus statement^[12], a first six-month period of DAPT (aspirin and clopidogrel), followed by SAPT indefinitely is recommended. Although this

protocol has been tested only for both the WATCHMAN[™]^[17] and the Amulet^[36] devices, it is nowadays applied for all LAAO devices. A shorter DAPT duration (1-3 months) followed by SAPT may be considered in patients at high bleeding risk. In the case of prohibitive bleeding risk, shorter antithrombotic regimens, or even no therapy at all, may be considered, after careful evaluation.

After the first period (3-6 months or lower) of DAPT, SAPT is the treatment of choice for patients undergoing LAA percutaneous closure. There is no definite consensus whether SAPT should be carried on indefinitely: however, in accordance with Glikson *et al.*^[12], SAPT should be prescribed indefinitely or at least for the first year after the procedure. Aspirin is generally the drug of choice for long-term treatment, unless contraindicated.

Antithrombotic therapy suboptimal or complicated LAA closure

The most common complications after LAAO are device-related thrombosis (DRT) and incomplete occlusions. TEE is the most accurate way to check for both complications; however, it is not systemically performed after LAAO, especially when a good procedural result is obtained.

DRT has been a historically rare complication of percutaneous LAA closure, ranging from < 2% to 5%^[37]. However, according to data published more recently, DRT prevalence may complicate up to 38% of LAAO procedures^[38]. DRT exhibits an increased risk of all-cause mortality and stroke: these patients' thromboembolic risk is estimated to be even higher than what would be expected by their baseline CHA₂DS₂-VASC score^[39,40]. DRT may appear even months after LAAO and no strong correlation with ongoing antithrombotic treatment has been found^[39]. Anticoagulation with subcutaneous heparin or OAC until thrombus dissolution is the treatment of choice for DRT^[12]; however, it poses a significant dilemma in patients with an absolute contraindication to OAC. Sedaghat *et al.*^[39] recently demonstrated that DRT resolution may be achieved even with other antithrombotic therapies, but no strong evidence exists.

Incomplete occlusion of the LAA may be procedure related or may be secondary to delayed or incomplete endothelialization of the device. Despite being made of a deformable material such as nitinol, devices come in a finite number of sizes and usually with a circular shape: therefore, they may not adapt correctly to each LAA anatomy which typically exhibits an oval orifice. Small (< 5 mm at TEE evaluation), incomplete occlusions of the LAA are generally clinically irrelevant and may resolve spontaneously over time; therefore, OAC therapy would not be useful^[41]. Moreover, even in larger incomplete LAA occlusions, OAC does not seem to be associated with stroke risk reduction^[41].

Therefore, regardless of complete LAA exclusion, no strong recommendation about adjunctive OAC after the procedure exists. However, four weeks of anticoagulation with low-molecular-weight heparin or VKA, if tolerated by the patient, followed by trans-esophageal echocardiogram reevaluation, appears to be a reasonable therapeutic approach in the case of incomplete LAA exclusion or thrombosis^[42].

GAPS IN EVIDENCE AND FUTURE PERSPECTIVES

The first and main gap in evidence is that initial randomized controlled trials comparing LAAO and anticoagulation showed good procedural results, and device performance emerged as non-inferior as compared to standard medical therapy in the overall population^[13,14]. However, percutaneous LAA occlusion is still considered (in both guidelines and clinical practice) as an option for patients with absolute contraindication to oral anticoagulant therapy or for those with prohibitive bleeding risk. A tendency toward a more liberal use of the procedure was registered in real world practice, reinforcing doubts about the non-receipt of evidence in the guidelines.

Second, one of the main gaps in evidence is that no trial randomizing patients to either LAAO or OAC exists. Therefore, LAAO does not have a Class I recommendation in current guidelines. The ASAP-TOO trial, randomizing patients unsuitable for OAC to receive either LAAO or APT, was interrupted for poor enrollment. This reflects the fact that LAAO is nowadays so popular and appears to be so safe that no clinician wants to risk randomization to the APT arm. Hence, registries are fundamental and represent the main source of data regarding LAAO procedures and different occlusion devices.

Then, additional evidence is needed to assess the safety and efficacy of LAA closure devices with respect to DOACs. In fact, DOACs proved to be at least as safe and effective as warfarin in preventing stroke in non-valvular AF and are now widely used in this subset of patients. Initial data came from observational studies. Godino *et al.*^[43] showed comparable safety and efficacy between LAAO and DOACs in terms of thromboembolic and major bleeding events in patients with non-valvular AF at high bleeding risk, whereas another study found lower bleeding and mortality in LAAO rather than in DOAC patients^[3]. A first, non-inferiority RCT showed that LAAO was non-inferior to DOAC in preventing both ischemic and hemorrhagic complications in a high-risk cohort of AF patients^[44], but more robust data from larger studies are expected. The CLOSURE-AF (NCT03463317) is a prospective, RCT assessing the non-inferiority, and possibly superiority, of percutaneous closure of the LAA with respect to both ischemic and bleeding risk in high-risk patients *vs.* OAC (both DOACs and VKAs). It is going to be the largest trial ever conducted on this topic. Data are expected to be available in 2023.

Another debatable aspect is the type and duration of antithrombotic therapy after LAAO. The SAFE-LAAC (NCT03445949) trial is currently recruiting patients to evaluate the safety and efficacy of stopping DAPT after 30 days rather than at 6 months. Investigators are also going to evaluate potential differences in stopping all antithrombotic and antiplatelet agents six months after LAA occlusion *vs.* long-term treatment with single antiplatelet agent. The ANDES trial (NCT03568890) is also currently recruiting patients to compare DOAC *vs.* antiplatelet therapy for 8 weeks after percutaneous LAAO, for the prevention of DRT. Promising results about the efficacy of lower dose DOACs came from the phase IIb ADRIFT trial, showing lower thrombin generation after LAAO using rivaroxaban 10-15 mg daily rather than DAPT^[45], but new, larger trials are needed. The use of DOACs instead of antiplatelet agents in post-procedural antithrombotic therapy may seem counterintuitive: however, the lower bleeding risk of DOAC with respect to warfarin and the possibility of using reduced dosages might suggest a new role for anticoagulation in these patients. Moreover, in the light of the recent evidence coming from the LAAOS III trial^[30], LAAO could be considered an adjunctive therapy to anticoagulation to reduce ischemic risk, despite striking differences between surgical and percutaneous LAAO.

Other trials aim to perform head-to-head comparisons between LAAO devices analyzing safety, efficacy, and specific indications for different devices. The largest ongoing trial is the Amulet IDE trial which compares the Amplatzer device *vs.* the WATCHMAN™ device and whose initial results have recently been published^[15]. In total, 1878 participants have been enrolled worldwide and will be followed for 5 years after device implant, evaluating both stroke and bleeding risk, procedure-related complications, mortality, and device closure. The most relevant ongoing trials are summarized in [Table 2](#).

Moreover, no definitive consensus on the appropriate echocardiographic follow-up to assess device success and complications has been published: whether a standardized approach might be useful in adapting current clinical practice still has to be determined.

Table 2. On-going trials. Adapted and modified from the 2020 EHRA/EAPCI expert consensus statement update on catheter-based left atrial appendage occlusion^[12]

Trial name	Summary	Device	Intervention	Patients enrolled	Primary outcome(s)	Status	Estimated primary and study completion date
ANDES	8 weeks OAC vs. APT for the prevention of DRT	Not specified	DOAC vs. clopidogrel + aspirin	350	2-month DRT	Recruiting	September 2022 to September 2025
ASAP-TOO	WATCHMAN vs. SAPT/no treatment in NVAF patients with a contraindication to OAC	WATCHMAN	LAAO + ATT vs. unspecified APT	482	7-day device/procedural safety and time to first event of SSE	Active, not recruiting	December 2025 to December 2025
STROKE-CLOSE	LAAO vs. medical therapy for stroke prevention in NVAF after intracranial hemorrhage	Amulet	LAAO + 45 days of DAPT + ≥ 6 months of SAPT vs. OAC, DOAC, SAPT, DAPT, no therapy	750	Composite of SSE bleeding and all-cause mortality up to 5 years	Recruiting	May 2022 to May 2030
SAFE-LAAC	Short vs. extended post-implantation DAPT and 6 months of APT vs. long-term SAPT	Amulet	(1) 30 days vs. 6 months of DAPT (randomized) (2) 6 months of APT vs. longer SAPT (not randomized)	160	Composite of SSE, TIA, non-fatal MI, CV, and all-cause mortality, moderate-severe bleeding, and LAA thrombosis	Recruiting	January 2021 to January 2022
CLOSURE-AF	LAAO vs. (D)OAC for stroke prevention in NVAF	CE-mark approved LAAO devices	LAAO + APT vs. (D)OAC	1512	Survival time free of SSE, major bleeding, and CV or unexplained death	Recruiting	February 2021 to February 2023
Occlusion-AF	LAAO vs. DOAC for stroke prevention in NVAF	Amulet or WATCHMAN	LAAO vs. DOAC	750	Composite of SSE major bleeding and all-cause mortality up to 5 years	Recruiting	February 2024 to October 2030
SWISS-APERO	Amulet vs. WATCHMAN FLX	Amulet or WATCHMAN FLX	AMPLATZER Amulet vs. WATCHMAN/FLX	200	Composite of LAA patency at 45 days and the crossover from one device to the other during device implantation	Active, not recruiting	July 2021 to May 2026
WATCH-TAVR	Medical therapy vs. WATCHMAN in patients with NVAF undergoing TAVR	WATCHMAN	TAVR + medical therapy vs. TAVR + WATCHMAN	350	Composite of all-cause mortality, stroke, and bleeding	Active, not recruiting	November 2022 to November 2022
TAVI/LAA occlusion	Medical therapy vs. LAAO in patients with NVAF undergoing TAVR	Not specified	TAVR + medical therapy vs. TAVR + LAAO	80	Embolic events, major bleeding, and CV mortality	Active, not recruiting	May 2023 to May 2023
CHAMPION-AF	WATCHMAN FLX as an alternative to DOAC	WATCHMAN FLX	WATCHMAN vs. DOAC	3000	Non-inferiority for SSE and CV death at 36 months, non-inferiority for SSE at 60 months, and superiority for non-procedural bleeding	Recruiting	December 2025 to December 2027

OAC: Oral anticoagulant; CV: cardiovascular; DOAC: direct OAC; DRT: device-related thrombosis; APT: antiplatelet therapy; SAPT: single APT; DAPT: double APT; ATT: antithrombotic therapy; LAAO: left atrial appendage occlusion; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; SSE: stroke or systemic embolism; TAVR: transcatheter aortic valve replacement.

CONCLUSION

LAAO could be an alternative to anticoagulation in patients with non-valvular AF. While only two devices (WATCHMAN and AMULET) are both CE marked and FDA approved, other devices are commercially available in Europe, with high procedural success and a low rate of complications.

However, some issues remain debatable such as appropriate duration of post procedural antithrombotic therapy, differences between devices, or complication management.

DECLARATIONS

Authors' contributions

Conception and drafting of the manuscript: Maurina M, Villaschi A, Pivato CA

Supervised and provided technical and material support: Mangieri A, Chiarito M, Regazzoli D, Fazzari F, Bertoldi L, Briani M

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Ethical approval and consent for participation

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Technical Note

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Single-port robotic radical cystectomy with ileal conduit urinary diversion: technique and review of the early outcomes in literature

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Abstract

The introduction of the da Vinci single port (SP) surgical system (Intuitive Surgical, Sunnyvale, CA, USA) has meant a necessary evolution in the surgical techniques used to perform various Urologic surgeries, such as robotic-assisted radical cystectomy (RARC). In this paper, we describe a step-by-step technique for RARC with intracorporeal ileal conduit urinary diversion using the SP system at our institution and summarize early outcomes in the literature. The surgery was performed utilizing the standard institutional approach for radical cystectomy for the multiport robot, modified for the SP where appropriate. A total of 3 articles were found that included early patient outcomes after SP RARC. Including our institution, a total of 21 patients were included in the final analysis. The average patient age was 68 years old, 16 of the 21 patients were male, 13 of the patients had intracorporeal urinary diversions, the average operative time was 366 min with an average estimated blood loss of 185. The average length of stay was 5.4 days. Among these patients, there were three 30-day complications noted and five 90-day complications, all of which were Clavian II or lower. We conclude that RARC utilizing the SP approach is both feasible and offers several theoretical advantages over the open and multiport approaches, but further study is necessary before advocating for widespread adoption of this modality.

Keywords: Single-port, robotic cystectomy, radical cystectomy, minimally invasive surgery



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INTRODUCTION

Muscle-invasive bladder cancer is an aggressive disease associated with high morbidity and mortality, and is primarily treated with radical cystectomy with multiple possible avenues for urinary diversion, including the ileal conduit urinary diversion or the orthotopic neobladder. This is classically done in an open fashion with the open radical cystectomy (ORC); however, with the increasing popularity of robotic surgery for pelvic surgery, there is growing interest in robotic-assisted radical cystectomy (RARC) as a minimally invasive alternative, with the use of the robot for radical cystectomy increasing from 16.7% in 2010 to 25.3% in 2013 in the United States^[1]. The robots typically utilized for RARC include multiport generations of the da Vinci platform, including the da Vinci SI and XI systems.

The da Vinci single port (SP) robotic system (Intuitive Surgical, Sunnyvale, CA, USA) is the most recent robotic platform approved by the FDA in 2018 for urological surgery, and was designed with several modifications to the previously available multi-port robotic systems. The SP system combines the camera and all instrument arms into a single port, allowing surgery to be performed using a single incision. Other notable features include a relocation feature that allows the operator to reach all abdominal quadrants by moving the entire trocar with the attached arm around its fulcrum, and a virtual navigator that provides real-time monitoring of the relative position of the instruments, even when off the visual field. This allows for greater control of the instruments and safer positioning. Theoretical advantages of the SP platform over the multiport include improved cosmesis due to surgery being performed through a single incision. Fewer incisions also have a theoretical benefit of reduced pain and improved visualization in a narrow space such as the pelvis. Retrospective studies on robotic prostatectomy have already shown an advantage in terms of pain scores after surgery and length of stay, with comparable outcomes^[2,3].

This article illustrates the technique performed utilizing the SP robotic system for the robotic-assisted laparoscopic radical cystectomy with ileal conduit urinary diversion in a male patient. To date, there are only three other published papers detailing the use of the SP robot for RARC, and no noninferiority studies comparing the SP RARC to multiport RARC. We provide a step-by-step technical approach to surgery with special attention paid to technical modifications from the multi-port technique.

METHODS

We provide a review of our technique for single-port radical cystectomy based on the experience from our institution. A video of the procedure is available as well. A review of early outcomes has been carried out through a retrospective analysis of clinical documentation. A systematic review of the literature outcomes was performed via a broad search of PubMed using the following keywords: da Vinci SP, single port robotic cystectomy, and radical cystectomy. We included a single patient from our institution, who was chosen according to standard patient selection for RARC, including the ability to tolerate pneumoperitoneum and steep Trendelenburg, BMI < 30 kg/m², and lack of prior pelvic radiation or trauma^[4].

Step-by-step surgical technique

Patient positioning and port placement

After induction of general anesthesia, the patient is positioned in the standard positioning for robotic pelvic surgery, specifically the dorsal lithotomy position with arms tucked, extremities padded and secured, and the bed in steep Trendelenburg. After the patient is prepped and draped in the normal sterile fashion, a Foley catheter is placed. A 2.5 cm incision is then made inferolateral to the umbilicus, approximately 1/3 of the distance between the umbilicus and iliac crest, and the Hasson technique is used to dissect through layers of fascia to access the abdominal cavity. Of note, this incision is later used as our stoma site for ileal conduit creation. We then insert an Alexis retractor into this incision site and attach the GelPOINT

advanced access platform (Applied Medical, Rancho Santa Margarita, CA, USA) with the SP Cannula to the Alexis. The abdomen is then insufflated to 15 mmHg, and carefully surveyed to identify any abdominal adhesions. We then place 2 additional trocars under direct vision, specifically a 12 mm port (to which an AirSeal is attached) approximately $\frac{2}{3}$ of the distance between the umbilicus and left iliac crest and a 5 mm assistant port halfway between the umbilicus and the 12 port. The SP robot is then side-docked.

General considerations

The SP RARC technique largely follows the standard multiport technique with RARC, with several key adjustments, notably the positioning of the robotic instruments. We begin with the monopolar scissors at the 3 o'clock position, Cardiere forceps at the 6 o'clock position, bipolar forceps at the 9 o'clock position, and the camera at the 12 o'clock position. Instruments are switched periodically to allow for optimal retraction depending on the specific step of the procedure performed.

Identification of the ureters

We locate the ureters bilaterally by incising the overlying peritoneum just lateral to the medial umbilical ligament and dissecting down to the level of the common iliac artery. The Cardiere forceps at 6 o'clock are useful for holding traction on the ureters and pushing the bowel medially during this dissection, which can be completed without the bedside assistant. Once the ureters are identified, they are placed on vessel loops and dissected down to the ureteropelvic junction, at which time they are clipped with two Hem-o-lock clips (Weck Closure Systems, Research Triangle Park, NC, USA) and divided.

Anterior and posterior bladder dissection

The LigaSure device is then used to divide the obliterated umbilical arteries bilaterally and the tissue lateral to the ureters. The bipolar forceps at 9 o'clock are used to lift the bladder, the Cardiere at 6 o'clock is used to provide downward traction on the bladder, and the monopolar scissors at 3 o'clock are used to open up the endopelvic fascia. The posterior peritoneum is then incised over the rectum, connecting the two entry points into the endopelvic fascia. The seminal vesicles are then identified and elevated, and the posterior plane between the rectum and bladder is bluntly dissected out. The LigaSure device is used to divide the superior vesical arteries bilaterally, taking care to stay below the seminal vesicles and ureteral stumps bilaterally. This dissection plane is taken all the way down to the prostate apex. We then divide the median and medial umbilical ligaments using the LigaSure device and drop the bladder into the pelvis. After the apex of the prostate is dissected, we switch our 3 o'clock and 9 o'clock instruments out for robotic needle drivers and oversew Santorini's plexus using 2-0 V-Loc suture in a figure-of-eight fashion. We then replace our monopolar scissors at 3 o'clock and bipolar forceps at 9 o'clock and divide Santorini's plexus. Next, we dissect out and free the urethra. The Foley catheter is clipped with a Weck clip to keep the balloon inflated to avoid spillage of bladder contents. The remaining lateral attachments of the prostate are then divided in a modified nerve-sparing fashion with bipolar cautery. Once the specimen is completely freed, it is placed in a 15 mm entrapment sac and set aside.

Pelvic lymphadenectomy

We then perform our bilateral pelvic lymphadenectomy, removing the external, obturator, internal, and common iliac lymph nodes bilaterally using Weck clips and bipolar cautery for lymphostasis. We periodically switch the positions of the Cardiere and bipolar forceps between the 6 o'clock and 9 o'clock positions as needed for better retraction of the lymph nodes, as the Cardiere provides a better medial retraction. The specimens are sent to pathology as right and left pelvic lymph nodes. The presacral space is then divided to allow for the passage of the left ureter under the mesorectum at the level of the sacral promontory. This dissection is performed with the Cardiere forceps at the 9 o'clock position to hold

traction on the sigmoid colon.

Intracorporeal ileal conduit creation

We begin the intracorporeal reconstruction portion of the case with the bipolar forceps at the 6 o'clock position, needle driver at 9 o'clock, and Cadere forceps at 3 o'clock. The left ureter is tunneled under the presacral space and sigmoid colon, with the Cadere forceps pulling the ureter through into the right retroperitoneum. The ileocecal valve is then identified, and a 3-0 Vicryl stay stitch is placed 30 cm from the valve, with a 15 cm segment of ileum marked out for the conduit. At this time, we switch the needle driver to the 3 o'clock position and Cadere to 9 o'clock, and monopolar scissors at 6 o'clock. Ligasure is used to take down the mesentery. The monopolar scissors are used to open up the bowel at both ends. The Endo-GIA stapler is advanced through the 12 trocar assistant port, and a stapled side-to-side small bowel anastomosis is performed at the first and second corners of each end of the bowel. This is first stapled across longitudinally, and then stapled again to seal the edge of the side-to-side anastomosis. Additional 3-0 Vicryl is used to buttress the staple line. We then orient the proximal segment of the ileal conduit towards the pelvis and the distal end towards the skin.

The right ureter is trimmed, with the distal ureter sent for frozen pathology. The ureter is then spatulated and anastomosed to the conduit in an end-to-side fashion with a running 4-0 Vicryl in a Bricker style. This is done with the Cadere at the 6 o'clock position to hold the conduit down and the bipolar forceps holding the ureter up - it must be noted that no assistant is needed for the anastomosis. We similarly prepare, spatulate, and anastomose the left ureter to the proximal end of the ileal conduit in an end-to-side fashion in the Bricker style.

Before each anastomosis is closed, we place single-J ureteral stents inside each ureter in the following fashion. Through the gel point, we insert a laparoscopic right angle holding a Motion wire inside the 2.5 cm right lower quadrant incision beside the robotic instruments. The wire is then passed from the distal to the proximal end of the conduit using the laparoscopic right angle, and pulled through with the Cadere forceps. The wire is then advanced into the ureter, and the single-J stent is advanced over the wire up the ureter until resistance is felt. The same step is used to place a stent up the ureter. After the conclusion of the ureteral-ileal anastomoses, the single j is secured to the distal part of the conduit with a long 0 Vicryl suture, the tail of which can be followed through the gel point. Eventually, a 15 round JP drain is inserted into the pelvis via the 5 mm port, which we suture to the skin with a 2-0 nylon. The robot is then undocked, the pneumo removed, and the specimen is removed through the SP incision. If needed, the incision is lengthened slightly to accommodate the sample. At this point, pulling gently on the 0 Vicryl previously placed, we can recover the distal part of the conduit, grab it with a ring forceps and bring it out through the SP incision. The stoma is then secured with 3-0 Vicryl to the fascia with seromuscular bites, and then the end of the stoma is matured, securing it to the dermis with seromuscular to mucosa to dermal sutures circumferentially, taking care not to suture the mesentery of the ileum. The stents are then trimmed and brought into a urostomy bag.

RESULTS

A total of 3 articles were found in the literature that summarized early patient outcomes after SP RARC^[5-7]. Including our institution, a total of 21 patients were included in the final analysis. The average patient age was 68 years old, 16 of the 21 patients were male, and 13 of the 21 patients had intracorporeal urinary diversions. The average operative time was 366 min with average estimated blood loss of 185. Average length of stay was 5.4 days. Among these patients, there were three 30-day 188 complications noted and five 90-day complications, all of which were Clavian II or lower [Table 1].

Table 1. Early clinical outcomes

Age	Sex	Op time	EBL	Nodal harvest	Length of stay	Preop path	Postop path	30 day complication	90 day complication
65	Male	411	250	4	7	pTa high volume	pT1N0	Clavian I	None
89	Male	245	200	10	6		pT1	None	
68	Male	285	250	16	5		pT2a	None	
67	Male	309	400	6	5		pT3b	Clavian II	
86	Male	242	150	18	6		pT2a	None	
70	Female	496	100	9	5	pT2 high grade, micropapillary features	pT4aN0 UC	Clavian I (n/v)	
75	Male	475	300	12	5	pT2 high grade UC	pT2bN0, marg neg, pT2 adenocarcinoma of prostate, ISUP grade 2	None	
71	Female	420	100	18	5	pT1 high grade BCG refractory	pTisN0 UC, marg neg	None	
71	Male	425	750	8	5	pT1 high-grade, inside bladder diverticulum	pT1N0, UC inside divertic, margins neg	None	
64	3 females, 9 males	387	117	11.9	5.4		2 T1; 10 T2		5

DISCUSSION

Urologists have always been early to adopt new technological advances in the field of surgery, and Urology was one of the first subspecialties to widely adopt the use of the da Vinci robot for various procedures involving the prostate, kidney, and bladder. Most notably, the use of the da Vinci robot has become so widespread for radical prostatectomy that it is now used for up to 85% of all radical prostatectomies^[8]. Urologists have been comparatively slower to adopt the robot for use in radical cystectomies, owing at least in part to the cystectomy being a more complex and technically challenging procedure, particularly due to the need for bladder reconstruction and urinary diversion. In addition, operative times tend to be longer for the robotic cystectomy without current proven benefit in terms of local recurrence rates^[9]. There is relatively little data currently out there on outcomes after SP RARC, owing in part to the newness of the SP system. Nevertheless, the addition of the da Vinci SP platform represents an exciting advancement in the realm of minimally invasive surgery, and with the rise in popularity and proven noninferiority of RARC compared to ORC, it is worth exploring and reporting the feasibility, safety, and outcomes of RARC utilizing the SP robot. The initial case reviews included in the study represent a promising start in demonstrating the safety and feasibility of performing RARC using the da Vinci SP robot.

Conclusion

RARC with intracorporeal ileal conduit urinary diversion can be performed in a safe manner with good preliminary outcomes using the new da Vinci SP platform. More studies with larger case volumes are required to determine distinguishing variables such as average length of procedure, length of hospital stay, complications, surgical margins, and post-operative local recurrence rates. Given numerous theoretical benefits of the SP system over multiport, including improved cosmesis, reduced pain requirements, and improved operative visualization in narrow spaces, it is an avenue of great interest in the field of minimally invasive Urology and warrants further exploration.

DECLARATIONS

Authors' contributions

Conceived the topic of study, provided guidance and expertise surrounding the technical steps of the procedure, and critically revised the final manuscript: Crivellaro S

Data gathering and literature review, data analysis and interpretation, and manuscript writing: Chen G

Availability of data and materials

Aside from the single patient from our institution included in the final data analysis of outcomes after SP RARC, all other data is officially published data accessible to any interested party. The data for outcomes outside of our institution is available through a basic PubMed search for SP RARC. Institution-specific data is available upon reasonable request.

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None.

Conflicts of interest

Dr. Simone Crivellaro is a consultant for Intuitive Surgical, Inc.

Ethical approval and consent to participate

Informed consent to participate in this study and similar studies was obtained from all patients undergoing robotic surgery at the University of Illinois at Chicago.

Consent for publication

Written consent for publication was obtained when the patient consented to participate in the study.

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Review

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Current status on robotic assisted myomectomy

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Abstract

Uterine leiomyomas are common benign solid tumors of the uterus. While the presence of fibroids is rarely life threatening, they are associated with symptoms affecting quality of life and fertility. Myomectomy is a standard fertility-sparing surgery which should be considered for women suffering from fibroid-related symptoms who do not desire hysterectomy or any alternative treatment option. While open surgery is thought to be reserved for large and numerous myomas, mini-invasive methods as laparoscopy and robot-assisted surgery have evolved in the hands of experienced surgeons to also deal with these more complex cases. Robotic myomectomy has its advantages in lower blood loss, fewer complications, and shorter hospital stay over open surgery, whereas the comparison outcomes with laparoscopic myomectomy are still uncertain. Advantages of the wristed instruments, three-dimensional vision along with the incorporation of correct surgical techniques could emphasize the benefits of the robotic assisted approach in large and numerous myoma cases. Careful and detailed assessment should precede the surgery to recognize risks and steps to reduce operation time, which tends to be the most presented drawback of robotic myomectomy. As the tendency of robot-assisted surgeries is growing, many authors share their experience or publish comparison studies with other surgical methods. Our article describes the current status concerning robotic myomectomy, reviewing publications from the past five years (2016-2021).

Keywords: Robotic surgery, robotic myomectomy, robot-assisted myomectomy, surgical techniques

INTRODUCTION

Uterine leiomyomas (uterine fibroids) are a common benign smooth muscle tumors of the uterus that



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affects up to 70% of women until reaching menopause^[1]. Risk factors include ethnicity, parity, early menarche, late menopause, family history, obesity, and hypertension^[2]. While the presence of myomas are rarely life threatening, they are associated with symptoms affecting quality of life such as abnormal bleeding, pelvic pain, and urinary tract problems^[3]. In addition, myomas might also be linked with adverse pregnancy outcomes such as infertility, preterm birth, or postpartum hemorrhage^[4]. Diagnosis is made based on pelvic bimanual examination, ultrasonography, magnetic resonance imaging, or hysteroscopy. According to the localization of the lesion (submucosal, intramural, or subserous), myomas are further defined by the International Federation of Gynecology and Obstetrics (FIGO) subclassification system to better describe their relation to the uterus and help select the appropriate therapeutical approach alongside other factors such as size, number of lesions, reproductive plans, surgeons' skill, *etc.*^[5]. Almost one third of women with myomas seek medical help and request treatment. The current medical strategies offer surgical interventions (myomectomy, hysterectomy, and occlusion of uterine arteries) or their alternatives (uterine artery embolization, high-frequency magnetic resonance-guided focused ultrasound, and ultrasound-guided radiofrequency ablation). Selective progesterone receptor modulators such as ulipristal acetate can be used as a preoperative option or as a pharmacological therapy to reduce symptomatology as an alternative to surgical treatment^[6,7].

Myomectomy is a standard fertility sparing surgical method and should be considered for women with fibroid related symptoms who do not desire hysterectomy. While open surgery (laparotomy) is thought to be reserved for large and numerous myomas, mini-invasive methods as laparoscopy and robot-assisted surgery have evolved in the hands of experienced surgeons to also deal with these more complex cases. As the tendency of robot-assisted surgeries is growing, many authors share their experience or comparisons with other surgical methods. In our center, we specialize on all surgical modalities, although in the majority of cases preferring mini-invasive methods. While hysterectomy is still our leading procedure on a robotic system, in the past years, the number of robotic myomectomies is rapidly growing, mostly for complex cases. Our goal when writing this article was to research the current literature to support our shift from laparoscopic to robotic myomectomies. Articles indexed with "robotic myomectomy, robot-assisted myomectomy" and published from 2016 to October 2021 were retrieved from PubMed and reviewed for relevancy. Our article presents the reader up-to-date consolidated information concerning the quickly evolving technique of robotic myomectomy.

COMPARISON STUDIES

Robotic myomectomy is favorable in less complications, blood loss and hospital stay compared to open surgery, while it is becoming a preferred modality in more complex cases to conventional laparoscopy.

The meta-analysis conducted by Wang *et al.*^[8] including 20 studies (2852 patients) compared robotic, laparoscopic, and open myomectomy. The results show that robotic myomectomy is associated with fewer complications and lower blood loss than the other modalities. It also showed lower conversion rate and less bleeding than laparoscopic myomectomy and lower postoperative pain score than open surgery. In a retrospective study by Ranes *et al.*^[9], longer operation time is stated as the biggest drawback in comparison with open surgery, which could outweigh shorter hospital stay. A mean operative time difference of 84 min (95%CI: 60.41-109.29) in favor of open myomectomy against robotic assisted was observed in a meta-analysis by Iavazzo *et al.*^[10]. On the other hand, robotic assisted myomectomy showed superiority in lower blood loss [92.78 mL/operation (95%CI: 47.26-138.29)], need for transfusion (981 patients; OR = 0.20; 95%CI: 0.09-0.43), total complications (1101 patients; OR = 0.31; 95%CI: 0.11-0.87), and length of hospital stay [1.84 days/patient (95%CI: 1.40-2.29)]. No significant difference was found in operating time, estimated blood loss, need for transfusion, number of complications, and length of hospital stay between robotic

assisted and conventional laparoscopic myomectomy.

In a review study considering open or mini-invasive way of entrance in myoma enucleation, comparable outcomes in estimated blood loss, complications, and duration of hospital stay were reached between laparoscopy and robotic surgery^[11]. The operative time of robotic myomectomy was stated as longer, as in previous studies. Demanding surgical skills for larger myomas and unfavorable localization and higher economic burden were stated as additional limiting factors for robotic myomectomy. The authors cited an older systematic review^[12], in which short-term benefits such as blood loss, need of blood transfusion, and hospitalization were significantly lower in robotic assisted myomectomy, while open surgery showed to be preferable in operating time and costs. Gingold *et al.*^[13] reviewed the myoma management in conventional vs. robotic assisted myomectomy. The outcomes of the reviewed studies show that robotic surgery was preferred in more complex cases, in which easier maneuverability of the wristed robotic instruments and three-dimensional visualization helped in better dissection, suturing, and application of hemostatic techniques. Nevertheless, these findings tend to be biased by surgeons' experience and inclination to select more difficult cases for robotic surgery and should not be considered as outcome-based evidence to prioritize robotic myomectomy.

When patients were questioned about their symptoms and health quality the morning before and one year after laparoscopic and robotic myomectomy, both groups showed a significant reduction in symptoms and improvement in quality of life without statistical difference between the two methods of surgery^[14].

In the last few years, the dominant comparison studies are between multiport vs. single-site/single-port robotic myomectomies. The consensus is that multiport myomectomy is preferred for larger myomas, while single-site is feasible for selected patients with less complicated cases, and both methods are associated with low rates of intra- and post-operative complications^[15,16]. In a very recent review, no significant differences were found in operating time, blood loss, and total complication rate^[17].

OPERATING TIME

Generally, robot-assisted surgeries tend to be longer because of the necessary docking of the robotic arms before the actual surgery begins. For myomectomies, the use of the wristed instruments should speed up the suturing time, which, in comparison with laparoscopy, is a common obstacle even in experienced surgeons. This hypothesis was disproved, when robotic myomectomies showed similar operating time with laparoscopic ones regardless of the number of myomas removed^[18]. It seems that the difficulty of docking and lack of tactile feedback during enucleation is compensated with easier and faster suturing in robotic myomectomy.

In a very recent study, factors related to the total operative time were body mass index (BMI), number of myomas, total myoma weight, location of dominant myoma, type of da Vinci robotic system (Xi vs. S), intraoperative uterine cavity exposure, blood loss, and total hospitalization period^[19]. To the contrary, all of the above-mentioned factors, except for the location of dominant myoma and type of robotic system, are also associated with console time. Age, parity, previous surgeries, surgical indication, and size of the dominant myoma were not associated with total operating time. In the analysis of 242 cases, the number of myomas (5-9 vs. ≥ 10) and surgeon's experience were the only two factors that were positively correlated with operation time. Furthermore, the number of myomas and maximal myoma diameter were positively correlated with estimated blood loss^[20].

Movilla *et al.*^[21] proposed a preoperative calculator to predict the total operative time of myomectomies. Factors significantly associated with the length of surgery are age, diabetes mellitus, uterine volume, number of myomas generally and those more than 3 cm, diameter of the dominant myoma, and surgeons' experience. On the other hand, BMI, hypertension, previous surgeries, location, and classification of the myomas do not affect the operative time.

The significantly reduced time of single-site procedure can be acquired by combining the advantages of the laparoscopic enucleation and robotic assisted suturing called hybrid robotic single-site myomectomy^[22,23].

The operating time also depends on the experience of the surgeon and the OR team. Robotic myomectomies have a steep learning curve, with the operating time significantly reducing after 10 cases^[24].

LARGE/HEAVY/MULTIPLE MYOMAS

Several case studies show the enucleation of huge myomas (the biggest being 28 cm and 3.2 kg), while pushing the limits of robotic assisted techniques^[25,26]. These cases confirm the efficiency, reliability, and safety of the robotic approach in well-selected cases regardless of the size of the fibroids. The major advantages of robotic surgery in comparison to abdominal is shorter hospital stay with faster recovery and less blood loss. Wristed instruments enabling a larger range of movements in a limited abdominal space blocked by the enlarged uterus and easier suturing of extensive uterine defects after enucleation are the assets of robotic surgery in contrast with laparoscopy resulting in lower conversion rate. A retrospective study of Lee *et al.*^[27] compared robot-assisted myomectomies (RAM) with abdominal myomectomies (AM) in myomas larger than 10 cm and heavier than 250 g. While the operating time was significantly longer in RAM than AM (164 min *vs.* 108 min), hospital stays were shorter (2.68 RAM days *vs.* 4.13 AM days). Short-term postoperative complications such as fever or bleeding were lower in RAM than AM (26% *vs.* 54%). In a retrospective study, outcomes of robotic myomectomies of patients with large myomas (> 10 cm) were compared with myomas < 10 cm operated by a single surgeon^[28]. While the largest myoma was 20 cm in diameter, operation time was the only significant difference between the two groups (263.4 ± 83.7 min *vs.* 219.1 ± 75.7 min, $P = 0.02$). Another comparison study between myoma size (≥ 9 cm *vs.* < 9 cm) showed significant increase in operation time (130 min *vs.* 92 min) and estimated blood loss (100 mL *vs.* 25 mL), while no major adverse outcomes were reported in either group^[29]. Jansen *et al.*^[30] retrospectively studied surgical approaches (abdominal, laparoscopic, or robotic) of myomectomies for extreme myoma burden (total specimen weight 436 g or ≤ 7 myomas). While the perioperative outcomes (estimated blood loss, blood transfusion, and complications) were similar in all modalities, mean operating time was the longest in robotic surgery (239 min) and mean hospital stay in abdominal surgery (2.2 days). Based on the analyses, the likelihood of complications increases in parallel with the myoma weight and number. The authors suggested preferring abdominal or laparoscopic approach in cases with extreme myoma weight and abdominal in cases of large number of myomas. On the other hand, Kim *et al.*^[31] compared 30 robotic *vs.* 13 open surgeries for the removal of ≥ 10 myomas. Operating times were longer in the robotic approach (360 min *vs.* 180 min), while length of hospital stay was shorter (2.5 days *vs.* 3.5 days). Because there were no conversions to laparotomy or any major complication, the authors suggested robotic approach to be an alternative to open surgery in cases with more than 10 myomas. Lee *et al.*^[32] recommended multiport robotic myomectomy with supraumbilical incisions in myomas larger than the umbilical level not only to ensure better cosmetic effect, but also to eliminate instrument and trocar collisions in single-port systems in a limited intrapelvic space.

FERTILITY AND OBSTETRICAL OUTCOMES AND RECURRENCE

Robotic surgery is a suitable myomectomy approach for infertile patients. In a retrospective study, more than half of the patients became pregnant with a 70% caesarean section rate without a report of uterine rupture^[33]. Uterine rupture was also not reported in a comparison study, in which long-term pregnancy and miscarriage rates did not significantly differ after robotic assisted, laparoscopic, or abdominal myomectomy^[34]. In a study where deep intramural myomas were enucleated, the pregnancy rate reached 75%^[35]. The same pregnancy rate (70%) after robotic myomectomy was published in a Canadian cohort with 84% successful delivery or ongoing pregnancy at the time of data collection^[36]. The risk of recurrence was 167% higher in laparoscopic myomectomy than in open surgery. The authors hypothesized that it is likely because of the extraction of small leiomyomas, which is less exhausting in manual removal than in the laparoscopic approach. The growth of residual myoma masses then results in newly diagnosed fibroids, which are considered recurrences^[37]. Considering the better flexibility of robotic instruments, enucleation of small myomas should be more accessible, leading to lower recurrence. Another reason for higher recurrence was found to be associated with the preoperative use of GnRH agonists therapy to decrease the size of myomas^[38].

SURGICAL TECHNIQUES

Safely extracting large and numerous myomas is often a challenge in minimal invasive surgery even for experienced surgeons. Moawad *et al.*^[39] presented a reproducible technique enabling fast and safe tissue containment and extraction. It consists of stringing numerous fibroids together with a barbed suture, containment using a Endocatch bag, extraction through the extended umbilical incision using the Alexis Containment and Extraction System, and finally the so-called paper roll technique for specimen extraction. Suprapubic incision is a similar technique, which serves for initial abdomen insufflation, later assistant's easy access for retraction or needle entry, and finally large tissue extraction^[40]. Contained manual morcellation is in comparison with electric power morcellation associated with shorter operation time but similar postoperative opioid pain relief treatment and length of hospital stay^[41]. Additionally, with the cessation of power morcellation, wound complications with the necessary mini-laparotomy for tissue extraction has not increased^[42].

Authors from South Korea proposed a new surgical technique called “locking suture on myoma (LSOM)” which replaces the tenaculum forceps, thus reducing the use of one instrument and lowering the total cost of surgery^[43]. In this technique, a locking V-Loc suture is applied on the myoma after its exposure and traction can be easily performed by grasping the thread. Further locking sutures are applied as the dissection advances between the myoma and myometrium. The retrieved myomas are easily collected and extracted by grasping the threads. LSOM was also shown to be more feasible for larger, heavier, and a greater number of myomas than using the robotic tenaculum forceps, emphasizing its use especially in single-site surgery.

A very interesting technique of submucosal FIGO 2 classified myoma without endometrial injury was presented in a case study^[44]. The authors recommended several steps to prevent penetration of to the uterine cavity. Proper preoperative and intraoperative imaging is crucial for planning the surgery and determining the correct site of myometrial incision. This is followed by cold cut careful preparation of the plane between the myoma and endometrium. Infusion of indigo carmine to dilate the uterine cavity aids in delineating the endometrial cavity during dissection.

Blood loss can be lowered without compromising surgical morbidity by the vascular control technique^[45]. This method uses vascular (bulldog) clamps to temporarily occlude the uterine arteries during the myomectomy. The maximal limit of occlusion time was set at 60 min with 5 min

reperfusion intervals every 20 min.

One of the technical disadvantages of the robotic system is the lack of haptic feedback of the instruments. In myomectomy especially, the absence of tactile feedback can lead to longer operation time due to the necessary identification of intramural myomas with ultrasound and less accurate and destructive myometrial incisions above the myoma^[13]. Giannini *et al.*^[46] presented a device (wearable fabric yielding display) that can reproduce the stiffness of myomas *ex vivo*. When integrated into commercially available robotic systems, this device could lead to a better intraoperative identification of myomas with more precise surgery.

LEARNING CURVE AND ECONOMICS

Acquisition of a new robotic system and its maintenance cost are considered as the biggest drawback of faster expansion of robotic surgery worldwide. Despite the obligatory cost of purchasing the robotic system with its disposable instruments, implementation of correct strategies can reduce the costs of robotic surgery while maximizing its benefits. The most influential modifying factors which lead to the cost-effectiveness of robotic assisted surgeries are intraoperative and postoperative complications, length of surgery, and length of hospital stay, which are all related to surgeons' experience^[47].

Even though there are no recent data on cost comparison of robotic vs. standard laparoscopic myomectomy, information could be related from benign hysterectomy surgeries. Interestingly, after adjusting patient-level covariates such as uterine weight, age, BMI, and previous abdominal or pelvic surgery, the cost of robotic surgery vs. laparoscopy was not significantly different in two separate hospitals. It is important to point out that the surgeries were performed by experienced surgeons past their learning curve^[48]. Similar results were presented in a randomized trial^[49], where comparable cost could be attained between the two modalities if a robot is already a pre-existing investment.

Data from single-center experience with robotic single-site myomectomy show a very rapid learning curve^[50]. After 10 cases, port placement time and docking time significantly reduced, in addition to a higher number of retrieved myomas and lower hemoglobin decrease after surgery. When comparing with conventional laparoscopy, docking time needs to be assessed separately as it is an element that does not exist in laparoscopy. When looking at cases of robotic hysterectomies, console time has the most rapid learning curve followed by docking time. Even in the case of a well-experienced laparoscopic surgeon transferring to robotic surgery, suturing requires the greatest number of attempts to achieve stability^[51].

Given that suturing is a major part of myomectomy, the surgeon's experience is a crucial variable in operation time resulting in cost effectiveness, as stated in previous studies.

Many resident and young surgeons struggle to keep up with the rapid advances in surgical techniques, mainly due to a lack of time spent in the operating room. Surgical simulators have an important role in helping to master these techniques outside the operation theatre. While computer simulators are often expensive and not realistic enough, live simulations are often very basic and life-like models cannot reproduce complex cases. Towner *et al.*^[52] constructed a model of myomatous uterus with artificial blood perfusion and secured it in a training box. In the post-simulation survey, residents stated higher confidence and comfort performing minimal invasive myomectomy which could have a positive impact on the learning curve in real-life surgeries.

CONCLUSION

The use of robotic systems enabled the implication of the advantages of mini-invasive surgery even in more complex cases. As the conclusions of studies are still not consistent, robotic myomectomy tends to show superiority in many factors over laparoscopy and open surgery. Operating time and higher cost seem to be the major drawback, but with the application of the presented surgical techniques and steep learning curve these could be rapidly minimized. Robotic single-site surgery seems to be a further step to reduce morbidity and pain and enhance cosmetic outcomes of minimal invasive techniques. This latest surgical access seems to be a feasible and safe procedure for myomectomy, which could replace conventional laparoscopy and robotic multiport surgeries even in complicated cases.

DECLARATIONS

Authors' contributions

Made substantial contributions to concept and design of the article: Kiss I, Svobodova P, Karasek L, Svoboda B

Drafted the article: Kiss I, Svobodova P

Critical revision of the article: Svobodova P, Karasek L, Svoboda B

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Perspective

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Has robotic prostatectomy determined the fall of the laparoscopic approach?

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Abstract

Robotic-assisted laparoscopic prostatectomy (RALP) has revolutionised the surgical management of localised prostate cancer in the modern era. The surgeon is provided with greater precision, more versatile dexterity and an immersive three-dimensional visual field. The impressive hardware facilitates, for example, the dissection of the peri-prostatic fascia, whilst preserving the neurovascular bundle, or the suturing of the vesico-urethral anastomosis. Prior to RALP, laparoscopic radical prostatectomy (LRP) represented the first venture into the minimally invasive world. Associated with more cumbersome ergonomics, LRP has a significant learning curve compared with the robotic approach. There has been a paucity, until recently, of high-quality literature comparing outcomes between the two operations, including the attainment of the *Pentafecta* of survivorship: biochemical recurrence-free, continence, potency, no postoperative complications and negative surgical margins.

Keywords: Prostate cancer, robotic, prostatectomy, laparoscopic

Today, the majority of men with intermediate or high-risk localised prostate cancer, who are candidates for surgical intervention, will undergo a robotic-assisted laparoscopic prostatectomy (RALP). The robot has firmly cemented itself as the modality of choice for both patients and urologists.



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Prior to the current era of minimally invasive surgery, the standard approach was open radical prostatectomy. The postoperative morbidity associated with the procedure however led surgeons to explore less invasive approaches. Laparoscopic radical prostatectomy (LRP) subsequently gained traction with the prospect of smaller incisions, less bleeding, fewer postoperative complications and reduced length of hospital stay^[1]. The new anatomical perspective encountered, manipulation required for suturing and cumbersome ergonomics no doubt proved challenging, particularly for laparoscopic naïve surgeons. Perhaps akin to “painting one’s hallway through the letterbox” and associated with a steep learning curve, many urologists opted to continue their open prostatectomy practice. A more attractive option was needed.

Since the turn of the millennium, the emergence of robotic technology has led to a new dawn in urological practice. The first RALP was undertaken in 2000, by Binder *et al.*^[2], at the Department of Urology of Frankfurt University.

Perhaps a misnomer, a better description of the robotic approach would be “*enhanced laparoscopic surgery*”. Comprising a surgeon console, patient cart and vision cart, the surgeon is provided with improved ergonomics, more versatile dexterity, beyond that of the human wrist, and enhanced three-dimensional high-definition optics. The impressive hardware has been further complemented, in recent iterations, with innovative software such as tremor filtration and intraoperative fluorescence imaging. The *da Vinci* system, manufactured by Californian based company *Intuitive*, is synonymous with robotic surgery and has remained the market leader since launching in 1999. Prostatectomy lends itself to the robot. The improved visualisation, for the dissection of the peri-prostatic fascia, down the deep male pelvis, and the resultant precision it allows, facilitating the preservation of the neurovascular tissue for nerve-sparing approaches, and the suturing of the vesico-urethral anastomosis. The anatomy of the prostate is so clearly visualised and appreciated. Ashutosh Tewari offers a helpful analogy whilst arguing the case for the robotic approach, with its improved visuals, in the Wall Street Journal (2018): “*When Swiss watchmakers start working in the dark, relying on tactile feedback and not magnifying glasses, then we’ll believe that surgery should be done by touch and not by direct visualisation of the anatomical structures*”.

The training of the future generation of minimally invasive surgeons is complimented with robotics. The learning curve is significantly less daunting and steep, with reported minimum numbers of 40 compared to 200-750 cases for RALP and LRP respectively. Even for the laparoscopic naïve surgeon, following the completion of 100 RALPs, the evidence would allude to a significant reduction in operating time, estimated blood loss and complications^[3]. Another aspect of the debate to consider, and perhaps not greatly acknowledged, is the impact operating might have on our physical health. A significant number of surgeons report musculoskeletal discomfort, impairing longevity and potentially catalysing early retirement. The awkwardness associated with the laparoscopic approach contrasts with the adjustable robotic surgical console. Surgeons when surveyed are in agreement; robotic surgery is a more comfortable experience that enables mitigation of these occupational ailments^[4].

Fundamentally it is the patient who should derive most benefit from any difference between techniques. The *Trifecta* of prostate cancer survivorship consists of (1) biochemical recurrence-free (2) urinary continence and (3) sexual potency. A *Pentafecta* has more recently been proposed that includes (4) no postoperative complications and (5) negative surgical margins^[5].

To date, there is a paucity of high-quality literature assessing these 5 pillars of outcome between RALP and LRP. The *LAP01* (2021) Randomised Controlled Trial attempted to address this. Heralded as the first patient blinded, multi-centre and multi-surgeon study (RALP *n* = 586, LRP *n* = 196). Given the widespread

acceptance of RALP in Germany, both patients and families tend to self-select the robot. Stolzenburg *et al.*^[6] randomised at a ratio of 3:1, in favour of RALP, to combat this. Superior continence rates, defined as “no use of pads or use of a single safety pad”, at 3-month follow-up were demonstrated with RALP (54% vs. 46%, $P = 0.027$). This difference was amplified when adjustments were made for bilateral nerve-sparing approaches (66% vs. 50%, $P = 0.005$). Secondary outcomes included continence rates as assessed via the validated *International Consultation on Incontinence-Short Form Questionnaire* (ICIQ-SF). Again, a significant difference was demonstrated at 3-month review with RALP (ICIQ sum scores $P = 0.003$). Despite being primarily powered for assessment of continence recovery, recovery of potency (erections sufficient for intercourse) at early 3-month follow up did demonstrate a significant improvement with the robotic technique (18% vs. 6.7%, $P = 0.007$). No significant differences in early oncological outcomes were documented^[6].

Prior to LAP01, Asimakopoulos *et al.*^[7] (RALP $n = 64$, LRP $n = 64$) illustrated a significantly improved 12-month evaluation of capability for intercourse (77% vs. 32%, $P < 0.0001$) with RALP compared to LRP in their single surgeon series. The improved potency was not associated with impaired oncological outcomes^[7]. Porpiglia *et al.*^[8] (RALP $n = 60$ and LRP $n = 60$) demonstrated improved 1-year urinary continence rates (95% vs. 83.3%, $P = 0.042$) and more favourable rates of erection recovery at 1-year, among pre-operative potent patients treated with nerve-sparing approaches (80% vs. 54.2%, $P = 0.020$).

In a recent meta-analysis, Wang *et al.*^[9] (2018) assessed 8 retrospective case series to date comparing the two techniques. Reduced rates of postoperative complications (including anastomotic leakage, anastomotic stenosis, rectal injury, urinary incontinence, and erectile dysfunction) and improved urinary continence rates, at 1-year follow-up, were reported with RALP ($P < 0.00001$)^[9].

On reflection, RALP will remain the standard-of-care approach. Postoperative complications are reduced, functional outcomes are improved (both continence and potency), and negative surgical margin rates are at least comparable^[10]. We await long term data post-prostatectomy, including biochemical recurrence-free rates between the techniques, and anticipate the late oncological outcomes from the LAP01 study. The robotic operative techniques will be honed, instruments enhanced, and further innovative software released, with an ever-increasing weaving of technology into the fabric of the operating theatre.

Albeit associated with significant up-front expenditure, when one considers the cumulative long-term health care costs, including the management of postoperative complications and functional outcomes, the argument is more nuanced, particularly in high-volume RALP centres. The higher index hospitalisation costs appear to be offset by the post-RALP health gains^[11]. There exists however, a considerable inequality gap between those centres across the globe that can afford robotic technologies and those that cannot. One hopes that over the forthcoming years challenger companies will emerge, competitive pricing ensues, and the robotic platform with its associated operating theatre costs will continue to dissipate.

Ultimately, let us not become too reliant on the impressive robotic technology at our disposal to achieve optimal postoperative outcomes. The attainment of the *Pentafecta* post-radical prostatectomy is reliant on a myriad of factors that include the comorbid status of our patients, the disease characteristics and most vitally, the guile, skill and experience of the urologist. The robot has not quite determined the fall of the surgeon.

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Authors' contributions

Made substantial contributions to article write-up: Hayes J, Vasdev N, Dasgupta P

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Review

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Minimally invasive surgery for gallbladder cancer at an expert center

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Abstract

In this article, we reviewed the techniques and outcomes of minimally invasive surgery for gallbladder cancer performed at an expert center. The techniques of laparoscopic extended cholecystectomy with the short- and long-term outcomes at our center were described. The short- and long-term survival outcomes of laparoscopic extended cholecystectomy are comparable to open surgery. Laparoscopic surgery is a safe, effective alternative for open surgery in the treatment of gallbladder cancer. The benefits of robotic surgery should be proven with further research.

Keywords: Gallbladder cancer, minimally invasive surgery, laparoscopic surgery, robotic surgery

INTRODUCTION

The treatment of gallbladder cancer (GBC) can be variable depending on the stage of disease. A variety of operations are performed, from simple cholecystectomy performed for T1a cancers to extended right hemihepatectomy and bile duct resection performed for more advanced cancers. There are several decisions for the surgeon to make^[1]. The first decision to be made is whether to proceed with surgery. The role of staging laparoscopy to aid this decision has been reported^[2]. Thereafter, the operator should decide whether



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to perform lymphadenectomy and its extent, whether to perform a liver wedge resection or a formal hepatectomy, and whether to perform a bile duct resection or not.

In the era of minimally invasive surgery (MIS), the treatment options for the surgeon are even more complicated. Currently, open surgery, laparoscopic surgery, and robotic surgery are all being performed^[3]. Therefore, it is necessary to evaluate the merits and demerits of these operation methods.

We have started a prospective study on “the laparoscopic approach for early GBC” in 2004, and have experienced a significant number of cases since. In this article, we review our history of MIS for GBC.

STEP BY STEP ADOPTION OF LAPAROSCOPIC SURGERY FOR GBC

Laparoscopic surgery for GBC was contraindicated for a long time, although cholecystectomy was the first laparoscopic surgery in the field of general surgery. With experience of MIS in various fields, we came to believe that laparoscopic surgery is beneficial for the patients in terms of less pain and rapid recovery with similar oncological outcomes. Therefore, we started a prospective study on laparoscopic surgery for early GBC in 2004. As this is the first prospective study for applying laparoscopy to malignant disease, we decided to plan the protocol to include only early GBC. Around 2010 was a time when many leading authors reported their initial experiences of advanced laparoscopy. Gumbs *et al.*^[4] reported encouraging results of three patients who received laparoscopic extended cholecystectomy, with no morbidity or mortality. In 2010, we also reported our “initial experience of laparoscopic approach with suspected gallbladder cancer”^[5]. Figure 1 shows our initial algorithm of patient care for suspected GBC. Endoscopic ultrasound was performed to determine liver invasion, and cases with liver invasion were treated with open radical cholecystectomy. In cases with peritoneal side tumors, intraoperative ultrasound was performed by experienced radiologists to rule out liver invasion. When there was no invasion, and the frozen section confirmed malignancy, laparoscopic extended cholecystectomy (which includes lymphadenectomy) was performed. Three trocars were used in the standard way for cholecystectomy. A thin layer of liver tissue was removed with the gallbladder to avoid bile spillage and to secure a safe margin. When frozen section confirmed malignancy, one or two trocars were additionally inserted for lymphadenectomy, and the pericholedochal, hilar, periportal, and common hepatic nodes were routinely dissected. Figure 2 shows the completion of lymphadenectomy.

After confirming the oncologic safety, laparoscopic surgery has been cautiously applied to GBC with liver invasion. To demonstrate this technique, we published a case report as a video article^[6]. Laparoscopic cholecystectomy with en bloc resection of the liver bed was performed, followed by regional lymphadenectomy. Ultrasonic shears were used to dissect the superficial liver parenchyma, and Cavitron Ultrasonic Surgical Aspirator was used to dissect the deeper parenchyma. The report has shown that laparoscopic lymphadenectomy and liver resection can be safely performed. With encouraging advances in surgical technique, we can move forward to extended cholecystectomy with liver wedge resection.

The indication for laparoscopy was further expanded to operations including bile duct resection. A video article of extended cholecystectomy with bile duct resection was published^[7]. The patient presented with postoperatively diagnosed GBC performed at another hospital. The cystic duct margin showed high grade dysplasia. Laparoscopic bile duct resection with lymph node dissection was performed. The bile duct was resected and retrocolic choledochojejunostomy was performed. The entire procedure of extended cholecystectomy, including lymphadenectomy, liver wedge resection, and bile duct resection, can be performed with laparoscopic procedure.

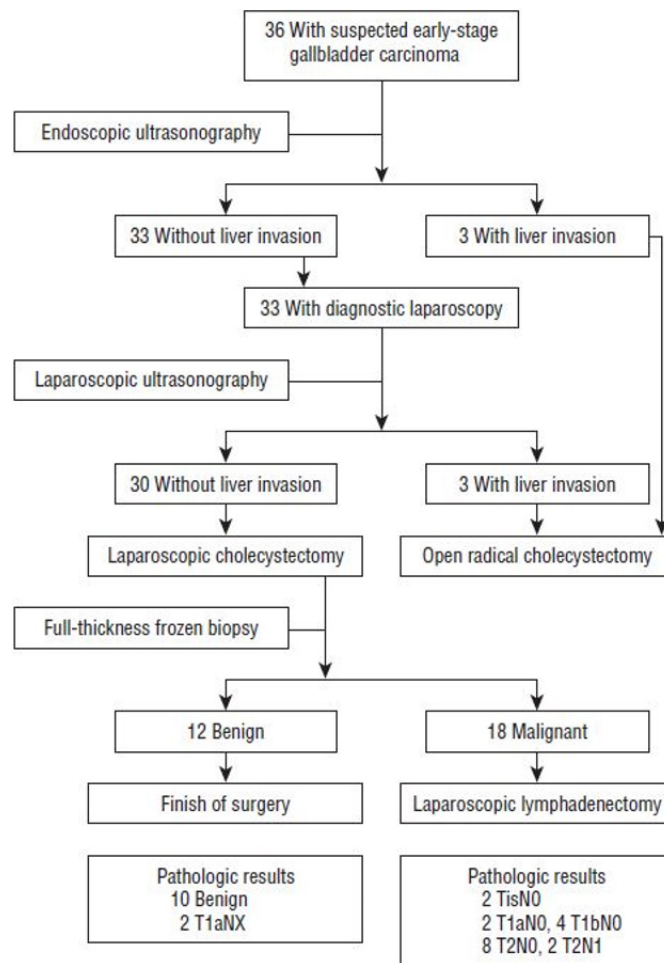


Figure 1. Algorithm for patients with suspected gallbladder cancer.



Figure 2. Completion of lymphadenectomy.

For technical tips, during laparoscopic extended cholecystectomy, a 3D flexible videoscope is usually used. This facilitates better orientation of the operative field, which makes equipment manipulation easy.

Additionally, when dividing small vessels, we prefer using a vessel sealing energy device rather than applying hemoclips. This technique shortens the operation time and can provide a cleaner operative field.

LONG-TERM OUTCOMES

In 2015, we published our long-term outcomes after laparoscopic approach for early GBC^[8]. During a ten-year period, 83 patients with suspected early GBC were enrolled in our prospective laparoscopic surgery protocol. Among these 83 patients, 45 patients had a pathologic diagnosis of GBC. The pathologic characteristics of the 45 patients are shown in [Table 1](#). After a median follow-up period of 60 months for 45 patients, the overall survival rate was 90.7%, and the disease-specific 5-year survival rate was 94.2% [[Figure 3](#)]. There were no cases with local recurrence at the lymphadenectomy site or the gallbladder bed. From these results, we concluded that MIS for GBC is an oncologically safe operation.

After accumulating 13 years of experience of laparoscopic extended cholecystectomy, we analyzed the oncologic outcomes of open vs. laparoscopic surgery for T2 GBC^[9]. During the period of 2004 to 2017, 247 patients with GBC were treated were at our hospital. Among these patients, 151 patients had T2 cancer. After exclusion, a total of 99 patients were analyzed. The types of operations performed on the open surgery (OS) group and the laparoscopic surgery (LS) group are shown in [Table 2](#). The OS group had more liver wedge resections than the LS group. The overall survival rates of the two groups are shown in [Figure 4](#); there was no statistical difference between the two groups in overall survival rate. The entire group was subdivided into T2N0 group and T2N1 group to compare the overall survival according to nodal status. There was no significant difference between the OS group and LS group, in both the T2N0 subgroup and T2N1 subgroup. This outcomes show that laparoscopic surgery is compatible with open surgery even in T2 stage GBC.

For more advanced lesions, such as more than T3, further comparative studies are necessary to evaluate the oncologic safety of the laparoscopic approach.

LAPAROSCOPIC SURGERY FOR GALLBLADDER CANCER: AN EXPERT CONSENSUS STATEMENT

Despite these encouraging results, and an increasing number of reports on the feasibility of the laparoscopic approach for the treatment of GBC, there was no consensus among experts. In September 10th, 2016, a consensus meeting was held in Seoul, Korea, and the expert consensus statement on laparoscopic surgery for GBC was established^[10]. Specific issues of this procedure were discussed among experts, such as concerns regarding laparoscopic surgery for GBC, application of laparoscopic surgery for GBC, laparoscopic extended cholecystectomy for GBC, and laparoscopic reoperation for postoperatively diagnosed GBC. The experts concluded that laparoscopic surgery does not worsen the prognosis of patients with early stage GBC, and that the postoperative and survival outcomes of highly selected patients were favorable.

Before this meeting was held, an international survey was undertaken of expert surgeons in the field of GBC surgery, and the results were published along with a review of the literature on the outcomes of laparoscopic surgery for GBC^[11]. The majority of surgeons agreed that laparoscopic surgery has an acceptable role for suspicious or early GBC, and that laparoscopic extended cholecystectomy has a value comparable to that of open surgery in selected patients with GBC. But the selection criteria for laparoscopic surgery for overt GBC, and the detailed techniques varied among surgeons.

Table 1. Pathologic characteristics of patients with gallbladder cancer

Variable	Data
T stage, <i>n</i>	
Tis	2
T1a	10
T1b	8
T2	25
N stage, <i>n</i>	
Nx	13
N0	27
N1	5
No. of retrieved lymph nodes,	
Median (range)	7 (1-15)
Tumor size, cm, median (range)	3.2 (1.2-11.5)
Histologic differentiation, <i>n</i>	
Well differentiated	29
Moderately differentiated	13
Poorly differentiated	3
Angiolymphatic invasion	8
Perineural invasion	4
R status, RO (%)	45 (100)

Table 2. Types of operations performed on the laparoscopic surgery and open surgery group

	LS group (<i>n</i> = 55)			OS group (<i>n</i> = 44)		
	T2Nx (<i>n</i> = 3)	T2N0 (<i>n</i> = 42)	T2N1 (<i>n</i> = 10)	T2Nx (<i>n</i> = 1)	T2N0 (<i>n</i> = 23)	T2N1 (<i>n</i> = 20)
C + LND	2	30	6		4	5
C + LND + LWR	1	11	4	1	17	14
C + LND + EHBDR		1			2	1

C: Cholecystectomy; LND: lymph node dissection; LWR: liver wedge resection; EHBDR: extrahepatic bile duct resection with Roux-en-Y hepaticojejunostomy; LS: laparoscopic surgery; OS: open surgery.

The results of perioperative outcomes and survival outcomes in this review are shown in [Tables 3](#) and [4](#), respectively.

PERSPECTIVES OF MIS INCLUDING ROBOTIC SURGERY

The development of minimally invasive surgery in the field of hepato-pancreato-biliary surgery was truly remarkable. A collective effort of surgeons has led to a wide dissemination of advanced laparoscopy in the hepato-pancreato-biliary field. Not only are the experts at high volume centers performing these high-end operations, but many surgeons around the globe now routinely perform laparoscopic hepato-pancreato-biliary surgery.

The advent of robotic surgery was another milestone in the history of surgery. Although many surgeons have readily acknowledged this technique, the benefits are still a matter of debate. Advocates maintain that robotic surgery is superior, due to the fine and precise movements and magnified 3D vision. Others are concerned about the loss of tactile feedback, limited array of instruments, and the cost issue. But even with this debate, many surgeons have already reported huge experiences in robotic

Table 3. Perioperative outcomes of published case series in which more than 5 patients with gallbladder cancer underwent laparoscopic extended cholecystectomy

Publication	Number of GBC patients	Indication	Open conversion (reason)	Operative time, min	Blood loss, mL	Complication, n (%)	Hospital stay, days
Cho <i>et al.</i> ^[5]	18	Primary	1 (portal vein injury)	190*	50*	3 (16.7)	4*
de Aretxabala <i>et al.</i> ^[12]	7	Completion	2 (LN metastasis, bile duct injury)	NA	NA	0	3
Gumbs <i>et al.</i> ^[13]	15	Primary (10), completion (5)	1 (CBD resection)	220	160	0	4
Agarwal <i>et al.</i> ^[14]	24	Primary (20), completion (4)	0	270*	200*	3 (12.5)	5*
Itano <i>et al.</i> ^[15]	16	Primary (16)	0	360	152	1 (5.2)	9
Shirobe <i>et al.</i> ^[16]	11	Primary (4), completion (7)	1 (CBD resection)	196	92	1 (9.1)	6
Yoon <i>et al.</i> ^[8]	30	Primary	1 (portal vein injury)	205*	100*	6 (18.8)	4*
Palanisamy <i>et al.</i> ^[17]	1	Primary	0	213	196	4 (28.6)	5

*Median. LN: Lymph node; GBC: gallbladder cancer.

Table 4. Oncologic outcomes of published case series that included more than 5 patients with gallbladder cancer who underwent laparoscopic extended cholecystectomy

Publication	7th AJCC stage	Curative resection, %	No. of retrieved LNs	Recurrence (local/systemic)	Survival
Cho <i>et al.</i> ^[5]	I (6), II (8), IIIB (2)	100	8*	0	NA
de Aretxabala <i>et al.</i> ^[12]	NA	NA	6	1 (systemic)	NA
Gumbs <i>et al.</i> ^[13]	I (4), II (8), IIIB (3)	100	4	2 (local, systemic)	NA
Agarwal <i>et al.</i> ^[14]	I (3), II (10), IIIA (6), IIIB (5)	100	10*	1 (local)	NA
Itano <i>et al.</i> ^[15]	I (3), II (13)	100	13	0	NA
Shirobe <i>et al.</i> ^[16]	I (3), II (6), IIIB (2)	82	13	2 (local + systemic, local)	5-year survival rate: 100% for T1b 83.3% for T2
Yoon <i>et al.</i> ^[8]	I (8), II (17), IIIB (5)	100	7*	4 (systemic)	5-year survival rate: 94.2%
Palanisamy <i>et al.</i> ^[17]	II (8), IIIA (1), IIIB (3)	100	8*	2 (systemic)	5-year survival rate; 68.75%

*Median. AJCC: American Joint Committee for Cancer; LN: lymph node; NA: not applicable.

pancreatectomy and hepatectomy.

When performing robotic pancreaticoduodenectomy, there is a definite benefit in facilitating anastomosis with higher degree of freedom. When pancreaticojejunostomy is performed by laparoscopy, there is limited freedom of instrument motion, and the needle holder manipulation is difficult. In contrast, when pancreaticojejunostomy is performed by the robot-assisted method, suturing can be performed almost the same as in open surgery, without any limitation of movement.

There have been several early reports of robotic surgery for GBC^[3,18,19]. In 2020, Belli *et al.*^[20] reported their experience on robotic surgery for 8 patients with GBC, with a mean operative time of 147 minutes and a 0% conversion rate. However, some issues need to be addressed. Surgery of GBC ranges from relatively simple cholecystectomy and lymphadenectomy to liver resection and bile duct resection. Early GBC may only require cholecystectomy with or without lymphadenectomy. Advanced cases may require extensive surgery with liver resection, and/or bile duct resection. If the operation is complicated, either laparoscopy and

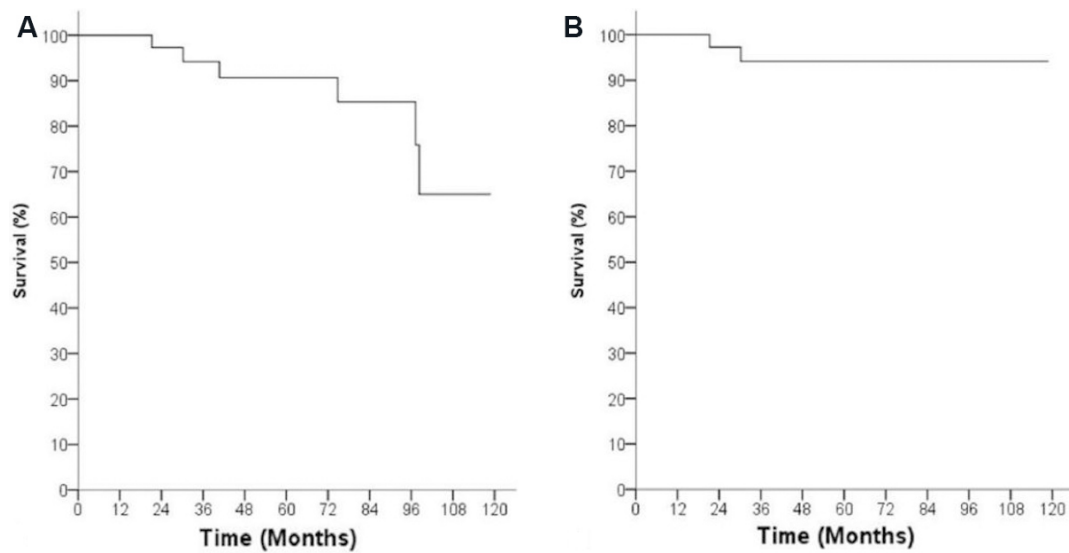


Figure 3. (A) Overall survival curve and (B) disease-specific survival curve for 45 patients.

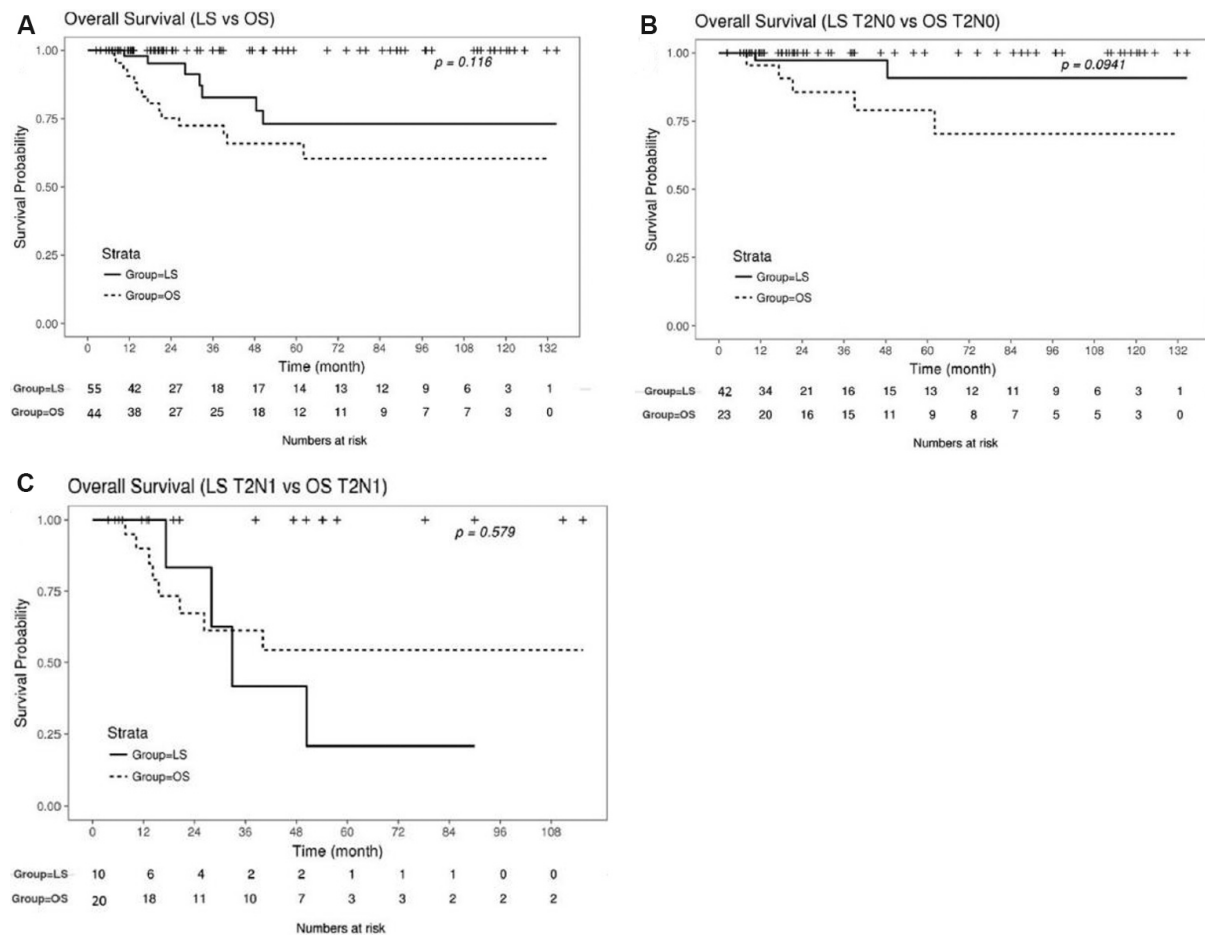


Figure 4. (A) Overall survival rate of laparoscopic surgery (LS) group and open surgery (OS) group; (B) overall survival rate of T2N0 patients of OS group and LS group; and (C) overall survival rate of T2N1 patients of OS group and LS group.

robot-assisted surgery can be chosen depending on each surgeon's preference. But in relatively simple surgery, the issue of cost-effectiveness matters.

Due to the monopoly of Da Vinci robotics, the cost of robotic surgery is still high. Many patients in Korea do not have insurance coverages for robotic surgery, forcing them to pay the high cost of robotic surgery out-of-pocket. For pancreas and liver surgery, the operative type is planned preoperatively. In contrast, in the treatment of GBC, the decision to proceed with a radical operation is often decided according to the results of the intraoperative frozen section pathology. Therefore, routine use of robots for any stage of GBC can be too expensive. Another demerit of robot-assisted surgery is the lack of proper instruments. When liver resection is required, parenchymal transection may be difficult, as there is no cavitron ultrasonic surgical aspirator in robotic surgery. Harmonic scalpel is frequently used as well for parenchymal transection in liver surgery. However, a robotic harmonic scalpel with endo-wrist movement has yet to be developed, diminishing the advantage of robotic surgery. In many cases of GBC, lymphadenectomy can be the only necessary procedure for an extended cholecystectomy. This procedure can be performed superbly with laparoscopic surgery. The benefits of choosing the robotic system for just the lymphadenectomy are questionable.

The dissemination of robotic surgery may be different from the dissemination of laparoscopic surgery. When laparoscopic surgery was first introduced, there was the very definite, obvious benefit of reduced scars and faster recovery compared to open surgery. The only concern was to ensure the oncologic safety. However, robotic surgery has no obvious benefits over laparoscopic surgery, which makes adoption of the procedure still a matter of debate, even decades after the introduction of robotic surgery.

Breakthrough innovations in the field of surgery are constantly happening. We are currently debating the pros and cons of laparoscopic and robotic surgery, but as is outlined in this editorial by professor Gumbs *et al.*^[21], artificial intelligence surgery is already here, albeit in limited ways. Refusing to accept new methods without any reason would slow down these advances in the field of surgery. But we must be critical in appraising the feasibility and safety of new methods, so that core values such as patient safety, oncologic feasibility, and cost-effectiveness are ensured. Perhaps with future developments of cheaper robotic systems with better surgical techniques, the benefit of robotic surgery may be shown later. But to date, there is insufficient evidence of benefit of the robotic system over laparoscopic surgery, in terms of extended cholecystectomy.

CONCLUSION

Laparoscopic surgery is a safe, effective alternative for open surgery in the treatment of gallbladder cancer. The benefits of robotic surgery should be proven with further research.

DECLARATIONS

Authors' contributions

Manuscript drafting: Lee JS

Made substantial contributions to conception and design of the study, editing, and administrative support: Han HS

Provided administrative, technical, and material support: Yoon YS, Cho JY, Lee HW, Lee BR, Kim MW, Jo YS

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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Labels, numbers, letters, arrows, and symbols in figure should be clear, of uniform size, and contrast with the background; Symbols, arrows, numbers, or letters used to identify parts of the illustrations must be identified and explained in the legend;

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All non-standard abbreviations should be explained in the legend;

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Tables should be provided in editable form like DOC or DOCX format (picture is not allowed);

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Explanatory matter should also be placed in footnotes;

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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

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8.1. Initial check

8.1.1. Initial manuscript check

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