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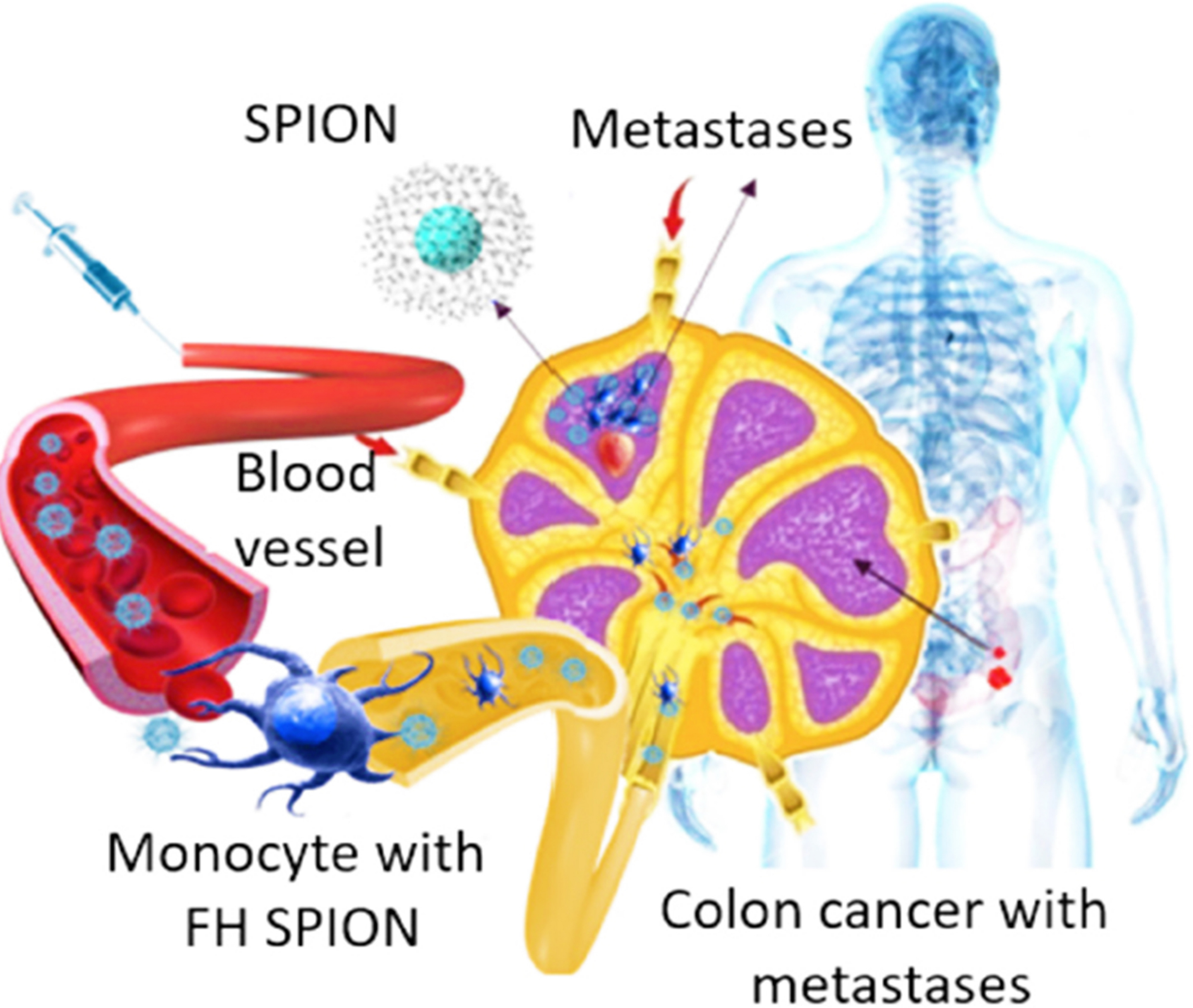

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CONTENTS

Mini-invasive Surgery

Case Report

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Paucisymptomatic gastric anisakiasis: endoscopical removal of *Anisakis* sp. larva

Rossella Palma[1], Simonetta Mattiucci[2], Cristina Panetta[1], Marilena Raniolo[1], Fabio Massimo Magliocca[3], Stefano Pontone[1]

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Abstract
Anisakiasis is increasing worldwide, even in Europe and in the Mediterranean region due to the increased practice of raw fish consumption. Usually, a detailed food history is the key to the diagnosis. A 52-year-old woman affected by pathological obesity underwent esophagogastroduodenoscopy (EGD) for a 1-year history of epigastric pain. In the gastric fundus, an *Anisakis* sp. larva, was casually detected. The nematode was successfully removed with a biopsy forceps. In this case, the finding of the parasite was casual, being detected during an accurate EGD performed for a 1-year history of epigastric pain in the patient.

Keywords: Endoscopy, epigastric pain, zoonotic parasite, *Anisakis*

INTRODUCTION

Anisakiasis is a fish-borne parasitic zoonosis associated with the consumption of raw or insufficiently cooked infected fish. The human disease is the result of the accidental ingestion of the third stage larva of the parasite that is infective to fish and squids. Most of the cases of Anisakiasis have been reported in Japan where there is a great consumption of raw fish, but the number of cases is increasing worldwide, even in Europe and in the Mediterranean region due to the increased practice of raw fish consumption. The anisakiasis is considered a rare disease even if the incidence is probably underestimated in many countries. As is reported in literature, the nematode is often hidden among gastric folds, and can be

 Palma *et al. Mini-invasive Surg* 2018;2:1 I http://dx.doi.org/10.20517/2574-1225.2017.40

Figure 1. The *Anisakis* larva visualization in the gastric fundus during retrovision maneuver close to the mucosal erosion

confused with gastric mucus and the gastric detection could be difficult using white light endoscopy[1]. For this reason, narrow band imaging is proposed in order to increase the nematode detection during esophagogastroduodenoscopy (EGD)[2]. In gastric anisakiasis, which is more frequent, symptoms occur just a few hours after raw fish consumption[3,4]. The typical clinical presentation is acute epigastric pain within 12 h after the ingestion of infected fish, occasionally accompanied by nausea, vomiting and fever[5]. Diagnosis is currently performed by the molecular identification of the parasite removed by gastric endoscopy associated to a seroimmunological assay. Also, a delayed allergic manifestation, named gastro-allergic anisakiasis (GAA)[6,7], may occur in association with rash, urticaria, isolated angioedema and anaphylaxis[8]. In this respect, Daschner *et al.*[6] described the GAA as an acute allergic reaction with symptoms of hypersensitivity appearing several hours after the ingestion associated with penetration of larvae into the gastric mucosa[9]. In addition, the presence of an IgE antibody response in individuals with no apparent symptoms has been also detected 1 month after the acute GAA episode[10]. It has been suggested that a variety of effector molecules form the allergic host defence response. One important step in the activation of this defence mechanism against *Anisakis* spp. and its antigens are the activation of Th2, leading to the secretion of cytokines, including interleukin (IL)-4, IL-5, IL-9 and IL-13 cells, which promote mast cell hyperplasia and eosinophilia. A recent study of Mattiucci *et al.*[11] has shown that Ani s 7-like and Ani s 13-like, detected in the sera samples, could be considered as major antigens in the diagnosis of allergic anisakiasis caused by *A. pegreffii.*

This report emphasizes the importance of investigating into raw fish ingestion in patients with signs and symptoms compatible with *Anisakis* sp. infection.

CASE REPORT

A 52-year-old Italian woman underwent upper elective endoscopy before having a sleeve gastrectomy. She was affected by pathological obesity and underwent EGD after 12 months history of epigastric pain and gastroesophageal reflux disease. She didn't have other symptoms such as nausea, vomiting, diarrhea or fever. Upper endoscopy showed gastric mucosa hyperemia with some micro-erosions in the context of antrum, middle body and fundus. In the gastric fundus, during retrovision maneuver, a mobile white thread-like worm, *Anisakis* sp. larva, was casually detected close to a mucosal erosion [Figure 1]. It was strongly adherent to the gastric mucosa and it could be confused with gastric mucus. The nematode was successfully removed by a biopsy forceps [Figure 2]. A bioptic fragment of the gastric tissue mucosa, including the nematode, was included in paraffin and histological sections were stained with haematoxylin-eosin revealing close to the gastric mucosa a nematode, at its larval stage. The diameter of the body, in a transerve section [Figure 3], was around 0.30 mm × 0.20 mm, with a thin cuticle, lacking lateral alae. Polymiarian muscle cells at both transverse and sagittal sections were visible; lateral chords were still visible despite the fact that the worm in the histological section appeared spoiled, and the intestine was circular with a triangular lumen. In

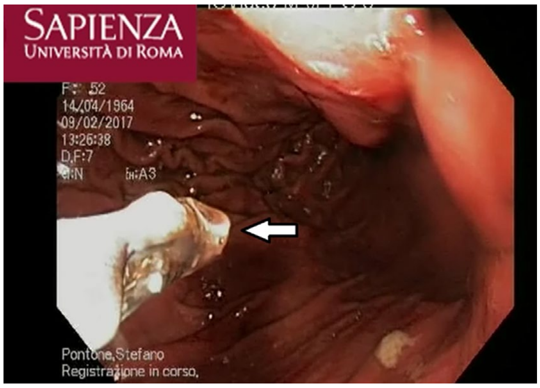

Figure 2. The nematode removal by biopsy forceps

Figure 3. Transverse section of *Anisakis* type I larva in the gastric mucosa. Scale bar 100 μm

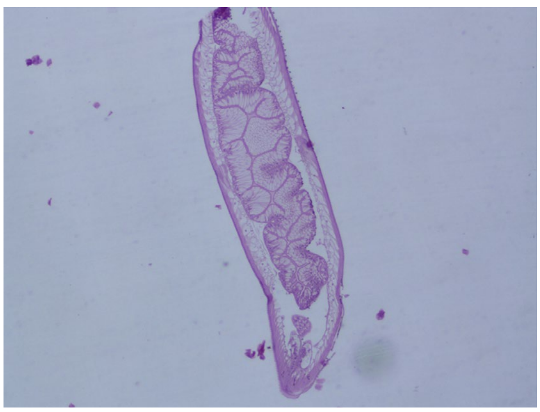

Figure 4. Sagittal section of *Anisakis* type I larva in the gastric mucosa. Magnification 40x

the sagittal section [Figure 4] two glandular cells found in the caudal end of the nematode were also visible. No ventricular appendix and/or intestinal caecum were found. According to those morphological features it was possible to refer the worm to a larval stage of a nematode belonging to the genus *Anisakis* [Video 1].

The patient reported she had eaten marinated raw anchovies at a sushi restaurant five days before the procedure and she described an intensification of gastric pain, in absence of other symptoms, after the ingestion of raw fish.

DISCUSSION

The gastric anisakiasis affects humans following consumption of raw or undercooked seafood. A detailed food history is the key to the diagnosis because the patients develop the typical symptoms shortly after ingestion of contaminated food. The clinical history can guide the diagnosis alerting the endoscopists to look for a nematode during an upper endoscopy. In absence of a detailed anamnesis, the correlation between the occurrence of gastrointestinal symptoms and raw fish ingestion could be very difficult. Gastric anisakiasis can be suspected based on the typical presentation, which is an acute severe epigastric pain few hours after the ingestion of infected fish. The symptoms usually develop within 12 h[5]. Other clinical manifestations include nausea, vomiting, and low grade fever. There are cases in which the patients present with hematemesis from gastric ulceration[12-14]. In addition to these impressive clinical presentations, there are some asymptomatic cases identified accidentally. The diagnosis could represent a challenging problem if a correct sampling and conservation strategy were not adopted. Furthermore, as previously mentioned, the gastric detection of nematode is not easily made because it could be confused with gastric mucus. Due to the rare occurrence of this disease, inexperienced endoscopists may easily overlook larvae, because they are usually hidden between the edematous gastric folds or blend in with the gastric mucosa[15]. Thus, the true incidence of the disease could be potentially higher than what is reported in the literature as cases can go undiagnosed.

When the clinical presentation doesn't suggest the *Anisakis* infection or lacks of a detailed food anamnesis only an experienced endoscopist performing an accurate EGD can detect the nematode.

In the case we have reported, the diagnosis was casual and the parasite was detected during an accurate EGD performed for a one-year history of epigastralgia in an obese patient, during a routine endoscopy before surgery, in absence of gastrointestinal acute suggestive symptoms and detailed food history. This report emphasizes the importance of investigating into raw fish ingestion before diagnostic upper endoscopy, especially in patients with signs and symptoms compatible with *Anisakis* sp. infection. However, the accurate and specific diagnosis of the etiological agents in human anisakiasis, should be performed by molecular methodologies, which was impossible to carry out in the present study. Indeed, currently, specific and rapid DNA assay tests such as the reverse transcription-polymerase chain reaction primers-probe systems are available to be performed on fragments of larval nematodes and bioptic tissues removed by endoscopy, but also on paraffine embedded parasites. Further, the immunoblotting assay of the patient serum, joined with anamnestic investigation of the patient and use of the molecular methodologies, has been recommended in the diagnosis of human anisakiasis.

DECLARATIONS

Authors' contributions

Manuscript preparation and data acquisition: Palma R
Data analysis and parasitological classification: Mattiucci S
Literature search: Panetta C
Data acquisition: Raniolo M
Anatomopathological classification: Magliocca FM
Study design and definition of intellectual content: Pontone S

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

The authors have obtained a written informed consent to publication, and a copy of the consent will be available if requested.

Ethics approval

The type of study does not require the consent of the ethics committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration when reporting studies on human beings.

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Mini-invasive Surgery

Original Article

Open Access

Upper gastrointestinal surgeon attitudes towards management of refractory gastroesophageal reflux disease in obese patients

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Abstract

Aim: The marked increase in prevalence of obesity has been associated with an increase in obese patients seeking surgical treatment for refractory gastroesophageal reflux disease (GORD). The management of GORD in such patients remains contentious with no published guidelines.

Methods: A snapshot 9-item online survey was undertaken to elicit professional opinions of UK surgeons regarding the surgical management of refractory GORD in obese patients.

Results: Eighty-two percent and 51% of surgeons performed more than 10 anti-reflux procedures and more than 10 bariatric procedures per year, respectively. Nearly 80 of responders would consider laparoscopic fundoplication as the preferred option for management of refractory GORD in patients with body mass index (BMI) of 30-34.9 kg/m^2. In contrast, 58% and 80% would discuss bariatric surgery as an alternative treatment option for refractory GORD in patients with BMI 35-39.9 and ≥ 40 kg/m^2, respectively. Moreover, a bariatric procedure was considered the preferred option by 74% of respondents for patients with BMI ≥ 40 kg/m^2 with refractory GORD, and by 58% for BMI ≥ 35 patients with refractory GORD and significant comorbidities. Eighty percent of surgeons agreed that laparoscopic Roux en-Y gastric bypass (LRYGB) was the preferred bariatric procedure for the management of obese patients with documented GORD.

Conclusion: Our survey demonstrated that amongst UK upper gastrointestinal surgeons, bariatric surgery, specifically LRYGB, was a preferred option for management of patients with a BMI ≥ 35 kg/m^2 and refractory GORD. Updated national guidelines are necessary to inform consensus on the management of GORD in obese patients.

Keywords: Obesity, morbid, bariatric, surgery, gastrooesophageal, reflux

INTRODUCTION

Gastroesophageal reflux disease (GORD) is defined as a group of symptoms and/or mucosal injury that occurs as a result of reflux of gastric contents into the oesophagus[1]. It is a frequently encountered and costly medical condition with an estimated annual cost of proton pump inhibitor use of nearly £500 million in England alone. The prevalence of GORD and obesity [body mass index (BMI) >30 kg/m^2] has increased significantly over the past three decades in the USA and Europe[2-6]. GORD is widely prevalent in obese patients; with increasing BMI considered a risk factor for developing the disease[7-16]. The marked increase in prevalence of obesity has been associated with an increase in obese patients seeking surgical treatment for refractory GORD[17]. The management of GORD in obese patients remains contentious with no consensus or published guidelines. Data are conflicting regarding the long-term efficacy of fundoplication in obese individuals compared with normal weight counterparts[18-22]. Nevertheless, most surgeons would agree that treatment of GORD in obese and non-obese patients requires different strategies[23]. The aim of this study was to elicit professional opinions of upper gastrointestinal (GI) surgeons towards the management of refractory GORD in obese patients.

METHODS

A snapshot 9-item online survey was undertaken between October and November 2015. Members of two UK specialist associations [Association of Upper GI Surgeons (AUGIS) and British Obesity and Metabolic Surgery Society (BOMSS)] were contacted via email and invited to participate in the survey [Supplementary Figure 1]. The questions were designed to characterize training and practice characteristics, experience, and subspecialty interest of respondents. Professional opinions were sought, regarding the optimal treatment for obese patients of varying BMI with medically refractory GORD and reasons for treatment choices.

RESULTS

A total of 451 specialist association members were emailed the link to the survey questions. All respondents were upper GI surgeons, of whom 51% were also bariatric surgeons. There was an even distribution of duration of practice as consultant surgeon amongst respondents (33% < 5 years, 27% had 5-10 years, 33% had 11-20 years, and 7% had > 20 years experience as consultant). Eighty-two percent regularly performed ≥ 10 laparoscopic and/or anti-reflux procedures per year and 51% admitted to regularly performing ≥ 10 bariatric procedures per year.

Sixty-one surgeons (79%) considered laparoscopic fundoplication the preferred option for management of refractory GORD in patients with BMI 30-34.9 kg/m^2 [Figure 1A]. However, only 21% and 11% would consider laparoscopic fundoplication as their preferred option for BMI 35-39.9 and ≥ 40 kg/m^2, respectively [Figure 1A]. Twenty-one surgeons (20%) considered anti-reflux surgery not a preferred option for refractory GORD in obese patients. Fifty-eight percent and 80% would discuss bariatric surgery as an alternative treatment option for refractory GORD in BMI 35-39.9 and ≥ 40 kg/m^2, respectively [Figure 1B]. Moreover, 74% and 58% of respondents considered a bariatric procedure the preferred option in patients, respectively, with BMI ≥ 40 kg/m^2 with refractory GORD, or BMI ≥ 35 kg/m^2 with significant comorbidities together with refractory GORD [Figure 1C]. Eighty percent of surgeons agreed laparoscopic Roux en-Y gastric bypass (LRYGB) was the bariatric procedure of choice for the management of obese patients with documented GORD [Figure 1D]. Reasons for bariatric surgery not being offered included lack of level one evidence (15%), lack of national consensus (26%), difficulty in referring patients for bariatric surgery (12%) or patient attitudes towards bariatric surgery (16%).

DISCUSSION

This snapshot survey sought to elicit UK upper GI surgeon attitudes towards the management of refractory GORD in obese patients. It demonstrated that upper GI surgeons still preferred fundoplication in patients with BMI 30-35 kg/m^2. However, they were less likely to offer fundoplication to patients at higher BMI. The

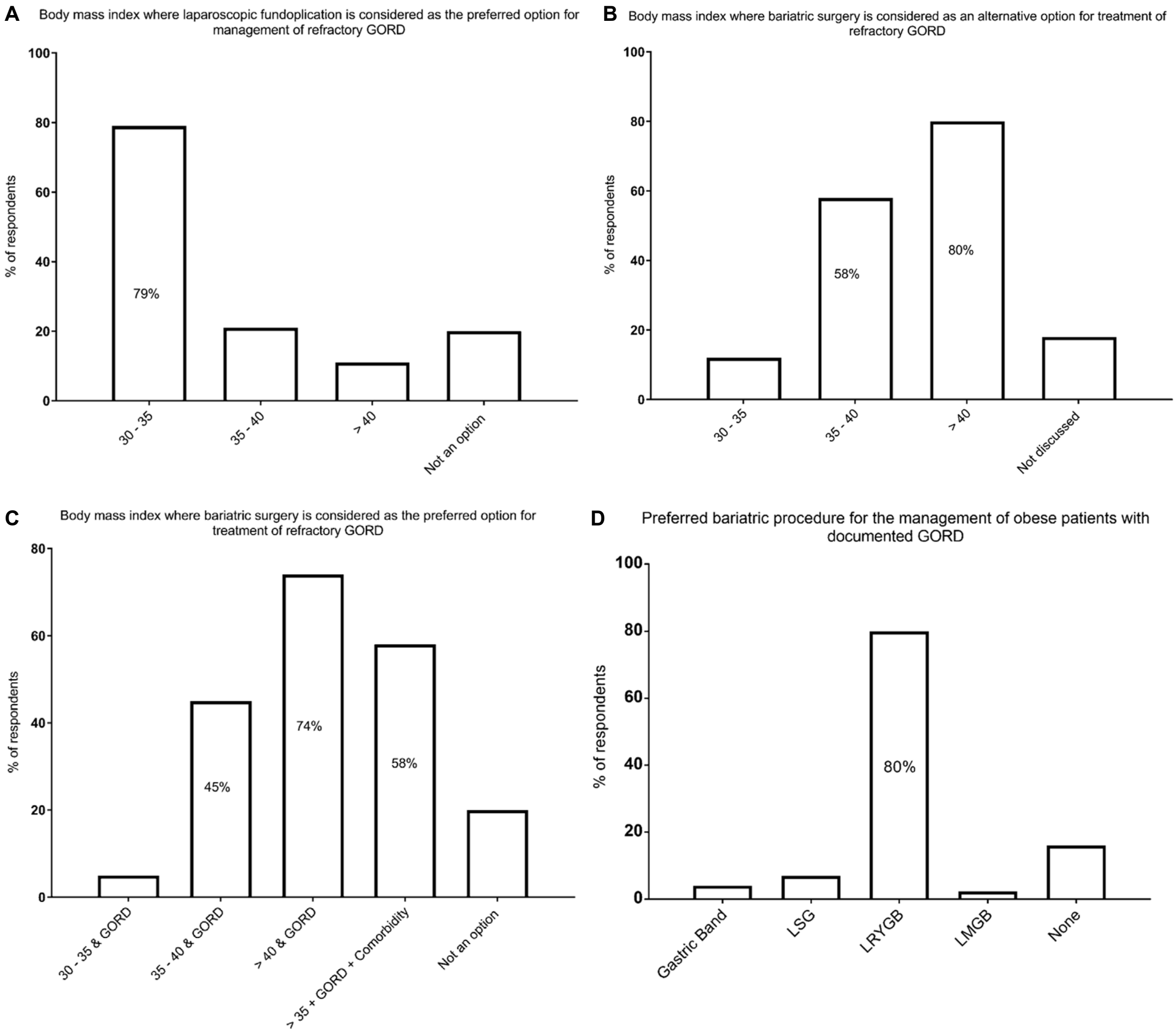

Figure 1. Summary of UK upper gastrointestinal surgeon attitudes towards management of refractory gastroesophageal reflux disease in obese patients. BMI: body mass index; GORD: gastroesophageal reflux disease; LSG: laparoscopic sleeve gastrectomy; LRYGB: laparoscopic Roux en-Y gastric bypass; LMGB: laparoscopic mini gastric bypass

majority of surgeons would consider a bariatric procedure the preferred option for management of refractory GORD in the morbidly obese and would discuss this as an option with their patients. The majority of respondents felt that LRYGB was the best option to treat medically refractory GORD in this patient group.

Anti-reflux surgery is recognised as the treatment option of choice for medically refractory GORD[24-26]. However, patient selection is essential to achieving a good outcome[27]. To date, few studies have examined the long-term efficacy and durability of traditional anti-reflux procedures such as Nissen fundoplication in the setting of severe obesity, and results have been conflicting[18-22]. It has been suggested that laparoscopic anti-reflux surgery is associated with a higher failure rate in obese patients because of intraoperative technical difficulties as well as increased intra-abdominal pressure postoperatively[28]. Nevertheless, others have reported equivalent outcomes in obese and normal weight individuals[17]. Obesity and GORD have a well-defined association due to several anatomic and hormonal pathophysiologic mechanisms[7-16]. Ultimately, while the medical and surgical treatment of GORD is advancing, there is a relative lack of specific studies examining novel GORD treatments in obese patients.

Existing data demonstrate LRYGB to be associated with significant improvement in GORD symptoms[26,27,29]. Many morbidly obese patients with GORD also suffer additional obesity-related conditions that are improved by LRYGB. For these reasons, most experts consider LRYGB a better treatment modality than traditional anti-reflux surgery in managing GORD as it also treats underlying obesity and associated comorbidities[26,27,29]. The benefits of LRYGB in BMI < 30 kg/m^2 patients is less clear and needs further study[26,27,29].

In this survey, the attitudes of UK surgeons was consistent with previous published international studies[27]. In a similar online survey by Pagé *et al*.[27] who examined the opinions of Members of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) regarding the management of GORD in the setting of obesity, most surgeons would offer laparoscopic anti-reflux surgery for patients with BMI < 35 kg/m^2 and symptomatic GORD, while LRYGB was considered the procedure of choice for those patients with BMI > 35kg/m^2[27]. However, Pagé *et al*.[27] suggest that morbidly obese patients with GORD, who would otherwise be best served with LRYGB, actually underwent Nissen fundoplication or no procedure at all due to financial limitations and policy exclusions. In contrast, UK surgeons would not consider bariatric surgery as their choice mainly due to the lack of national consensus and guidelines. Restrictions in commissioning in the UK may also have an impact if a significant number of patients were to undergo bariatric surgery primarily to manage reflux. The results of this survey may help inform surgeon practices pending development of much needed national consensus guidelines.

Limitations of this study include an 18% response rate, and that the opinions of specialty associations may not be representative of the wider UK surgical community. Finally, this study was designed to elicit surgeon opinions and attitudes and was not a randomised study comparing the two approaches.

In conclusion, this survey demonstrated bariatric surgery, specifically LRYGB, to be considered the preferred treatment option for BMI ≥ 35 kg/m^2 patients with refractory GORD. There is a need for published national guidance to inform clinical practice on the management of GORD in patients with severe and complex obesity.

DECLARATIONS

Authors' contributions

Manuscript preparation and data acquisition: Al-Khyatt W, Awad S, Leeder P
Data analysis and parasitological classification: Al-Khyatt W
Literature search: Al-Khyatt W
Data acquisition: Al-Khyatt W
Anatomopathological classification: Al-Khyatt W, Awad S, Leeder P
Study design and definition of intellectual content: Al-Khyatt W, Awad S, Leeder P

Data source and availability

All data are stored in a password protected hard drive and available on request via the corresponding author.

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Sherif Awad has received unrestricted educational and travel grants from Fresenius Kabi, Nestle Nutrition, Medtronic, Ethicon EndoSurgery, Merck Sharp &Dohme, Fischer &Paykel Healthcare Ltd, and BBraun. He has received honoraria and consultancy fees from Apollo Endosurgery, Merck Sharp &Dohme and Fischer &Paykel Healthcare Ltd. He has also completed a bariatric fellowship funded via an educational grant from Ethicon EndoSurgery (paid to the institution). Paul Leeder has received unrestricted educational grants from Ethicon, Medtronic and Allergan. He has received honoraria from Karl Storz and Allergan.

Conflicts of interest

The authors have no direct conflicts of interest to declare.

Patient consent

Not applicable.

Ethics approval

Not applicable.

Copyright

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Mini-invasive Surgery

Review

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Complications of robotic and laparoscopic urologic surgery relevant to anesthesia

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Abstract

Technology keeps advancing in this era allowing surgery to become less invasive in many surgical sciences. Besides these technological advances, minimally invasive procedures such as laparoscopy and robotic assisted laparoscopy are preferred widely around the globe by both surgeons and patients. Because of the increasing demand to laparoscopy and robotic surgery, anesthetists also should adapt to these specific surgical procedures. Carbon dioxide (CO_2) insufflation is applied in these procedures in order to provide working space and exposure to target organs. CO_2 insufflation (pneumoperitoneum if applied intrabdominally) and positional maneuvers such as steep Trendelenburg position is used in urologic laparoscopy and robotic surgery, which have vital effects on patient's physiology regarding cardiovascular, respiratory, renal, ocular and neurological systems. Special positions and unique surgical tools used in these procedures may hinder vital interventions such as cardiopulmonary resuscitation and open conversion. Comprehension of these pathophysiological effects and specific considerations is crucial to detect, to prevent and to manage serious complications that may occur during surgery.

Keywords: Anesthesia, complications, laparoscopy, pathophysiological changes robotic surgery, urologic surgery

INTRODUCTION

Minimally invasive surgery is now being applied more and more frequently in urology practice as it is in other surgical sciences. With the advances in technology, robotics had started to be used in surgery and robotic surgery followed the widespread use of laparoscopic surgery. Many oncological and reconstructive surgical operations are performed worldwide with laparoscopic and robotic assisted laparoscopic surgery.

Although the aim of the procedures and the results obtained with the application of laparoscopic surgical techniques seem similar, the physiological effects of laparoscopy are very different from open surgery; therefore minimal invasive surgery certainly requires a specific anesthetic management[1,2]. For laparoscopic and robotic assisted laparoscopic operations, pneumoperitoneum is essential to provide the working area. The most common gas to provide the pneumoperitoneum is carbon dioxide (CO_2). The metabolic profile created by the absorption of CO_2 gas and the effect of abdominal or retroperitoneal high pressures, especially on the respiratory and circulatory system, can compromise the anesthetic management of laparoscopic procedures[3]. This becomes even more complicated in operations where steep Trendelenburg position is combined, such as robotic radical cystectomy and robotic radical prostatectomy. Combination of pneumoperitoneum with steep Trendelenburg position in these operations may increase the risk of hemodynamic, respiratory and hemostatic disorders[3-5]. In order to provide the proper management of the patient undergone a laparoscopic or robotic assisted laparoscopic surgery and avoid the complications; one must thoroughly understand the effects of CO_2 pneumoperitoneum and Trendelenburg position.

PATHOPHYSIOLOGICAL EFFECTS OF PNEUMOPERITONEUM AND TRENDELENBURG POSITION DURING LAPAROSCOPY

For an adequate working space and exposure to the target area of the operation, initially pneumoperitoneum is provided and usually CO_2 gas is used for the procedure. Pressure levels change between 12-15 mmHg in most cases. However up to 20 mmHg pressures are reported in the literature[4]. CO_2 insufflation is applied through a Veress needle or through a trocar if open Hasson technique is used. In some procedures such as robotic radical prostatectomy or robotic radical cystectomy, applying Trendelenburg position may also be mandatory because the intestines might obscure the vision. In order to have adequate exposure; the bowels must be removed from targeted area of surgery by applying Trendelenburg position. But pneumoperitoneum (both by increasing the intra-abdominal pressure and by causing hypercarbia) and Trendelenburg position itself has considerable effects on cardiac, pulmonary, renal and cerebrovascular physiology[5-7].

Effects of carbon dioxide absorption

With the beginning of insufflation CO_2 gas starts to fill the cavity where the operation will be carried on. It is highly diffusible in the body and highly soluble in blood. CO_2 exposure may lead to hypercarbia. Hypercarbia increases with higher pressures and longer exposure times[7]. The respiratory system is the major way to excrete the CO_2. Pneumoperitoneum with high intrabdominal pressures and Trendelenburg position may affect the excretion of CO_2. Therefore, higher CO_2 pressure both increases the absorption and decreases the exhaustion. The dissolved CO_2 in blood increases H^+ ions and causes acidosis. Hypercarbia and acidosis decrease the cardiac contractility, make myocardium more sensitive to catecholamines and cause peripheral vasodilatation. But with the sympathetic activation caused by hypercarbia it finally leads to tachycardia and vasoconstriction[8]. During laparoscopic or robotic operations in urology both transperitoneal (TP) and extraperitoneal (EP) techniques are used. Although both approaches seem to have similar consequences there are minor differences observed during CO_2 insufflation. In their research comparing the effects of CO_2 insufflation on hemodynamics, oxygen levels and acid-base homeostasis in TP *vs*. EP robot-assisted laparosopic radical prostatectomy (RALRP), Dal Moro *et al*.[9] reported that, EP approach causes a higher absorption of CO_2, thus a more rapid acidosis. Although in both approaches there were similar operative times and there was even a less extreme Trendelenburg position in EP approach, EP RALRP was more relevant with CO_2 absorption and acidosis. A similar study by Meininger *et al*.[10] also reports that CO_2 absorption was more pronounced with EP approach than TP. However the reasons for these consequences seem to be multifactorial and have not been yet clarified[9].

Pneumoperitoneum and Trendelenburg position

TP approach is frequently preferred in urological surgery as it provides a familiar anatomic perspective to the surgeon and it is thought to be an easier technique to master at. However, EP approach may also be preferred, and both techniques have advantages and disadvantages. CO_2 insufflation to abdominal cavity creates pneumoperitoneum. CO_2 insufflation makes considerable pathophysiological affects by causing hypercarbia and acidosis. Apart from that pneumoperitoneum increases intra-abdominal pressure (IAP) which may cause serious cardiovascular, respiratory and neurological effects[5-7,11-13]. Trendelenburg position also effects negatively by decreasing pulmonary compliance and functional residual capacity[14-16].

Effects on cardiovascular system

The effects of pneumoperitoneum on hemodynamics is highly depended on the level of IAP, and patient position[12]. With the initiation of pneumoperitoneum mean arterial pressure (MAP) and systemic vascular resistance (SVR) increase > 25% and 20% respectively, however SVR returns to basal after providing Trendelenburg position[17]. Increased IAP decreases the venous return and cardiac output but Trendelenburg position reversely increases the venous return and it may neutralize this effect[18]. But of course these effects alter with the level of IAP. IAP lower than 15 mmHg causes increase in cardiac output by applying pressure to splanchnic venous bed and sympathetic stimulation caused by hypercarbia contributes by providing peripheral vasoconstriction and increasing cardiac motility. On the other hand IAP > 15 mmHg applies compression over inferior vena cava and preload decreases causing hypotension[18]. Another significant factor in laparoscopy that has effect on hemodynamics is vagal stimulation. Vagal stimulation may be initiated by peritoneal expansion caused by pneumoperitoneum, by direct stimulation of peritoneum with Veress needle or trocars or as a result of gas embolism (CO_2 embolism)[19]. Vagal stimulation may cause bradyarrhythmia (in a range from bradycardia to asystole) and hypotension[7,20]. Tachyarrhythmia may also be experienced as a result of sympathetic activation caused by hypercarbia[8]. The effects of pneumoperitoneum and Trendelenburg position on hemodynamics are usually well tolerated in patients with normal cardiac function, but it has been reported that even in elderly patients with ASA 2-3 risk or even in patients with underlying heart conditions such as aortic stenosis, laparoscopic operations may still be safely performed with adequate monitoring and being aware of possible complications[21,22]. High insufflation pressures and hypercarbia caused by long operative times or CO_2 venous embolism increases the risk of cardiovascular complications.

Effects on respiratory system

During laparoscopy insufflation increases IAP which causes an increase in peak airway pressures and a decrease in lung volumes and pulmonary compliance[23]. Particularly in operations such as RALRP or robotic cystectomy cephalad shift of diaphragm related to high IAP gets more severe by the addition of Trendelenburg position, because the abdominal contents push the diaphragm[23]. Eventually atelectasis may occur and functional residual capacity may decrease and a ventilation-perfusion mismatch may develop. These changes may lead to hypercarbia and hypoxemia. Moreover, high IAP increases the risk of barotrauma which may lead to pneumothorax or pneumomediastinum. These effects on respiratory system do not immediately return to normal postoperatively. Studies show that regaining full function of lungs may take 5 days postoperatively in patients without pulmonary disease, while it may take more than 5 days in patients with chronic obstructive pulmonary disease (COPD)[16]. Therefore patients with COPD should be advised to continue pulmonary rehabilitation even after being discharged.

Effects on neurological system

Pneumoperitoneum and Trendelenburg position are both found to increase the intracranial pressure (ICP)[5,13,24,25]. During pneumoperitoneum increased IAP prevents the venous return from lumbar venous plexus thus causing ICP to increase. Cerebral venous drainage is hindered and cerebral intravascular volume is increased. Due to these reasons ICP increases. Also combining pneumoperitoneum with Trendelenburg increases the ICP further and this may hinder cerebral oxygenation[26]. Kalmar *et al.*[27] examined patients undergoing RALRP which were exposed to prolonged steep Trendelenburg position and CO_2 pneumoperitoneum and suggested that it does not compromise cerebral perfusion. Though, it is advised to keep the patient in normocapnic range because regional cerebral oxygen saturation (rSO_2) is correlated with the increase in partial pressure of CO_2 ($PaCO_2$). If the patient has already an increased ICP caused by various reasons or there is a risk of cerebral ischemia inducing with pneumoperitoneum and applying Trendelenburg position may cause no toleration due to ICP increase and severe cerebrovascular complications.

COMPLICATIONS AND MANAGEMENT

Pathophysiological changes during laparoscopy and robotic surgery has been already discussed. Most of these effects are well tolerated if a proper anesthetic care is provided in healthy patients. But even in healthy patients undesired consequences may be experienced. In order to prevent serious morbidity and mortality management of complications should be taken seriously and a coordinated crisis plan should be ready to be executed. Patients should be properly monitored to understand the current situation, to maintain stability and to avoid the complications with the necessary interventions on time. Standard monitoring includes electrocardiogram, non-invasive blood pressure, pulse oximetry, end tidal CO_2 concentration and urine output. Also in major surgery, hemodynamically unstable patients or in patients with cardiovascular disease intra-arterial blood pressure may be monitored by arterial cannulation[21,28].

Cardiovascular complications

Cardiovascular complications related to laparoscopy begin to emerge with CO_2 insufflation. Hypotension, hypertension, arrhythmias and cardiac arrest may be encountered during laparoscopy. As the Trendelenburg position has the risk of increasing the risk of these complications, it may be wise to create the pneumoperitoneum in horizontal position rather than down-tilted[12]. CO_2 insufflation and positional changes should be applied gradually as sudden changes may affect hemodynamic stability. Monitoring IAP is also mandatory, because it is one of the main reasons of changes on hemodynamics. Keeping the IAP low may allow avoiding many complications related to carboperitoneum. IAP > 15 mmHg increases cardiovascular risk as inferior vena cava is compressed and eventually preload decreases. Additionally atropine might be administrated before the initiation of pneumoperitoneum or it may be kept ready for administration to prevent the brady-arrhythmias related to vagal reflex[12]. Acid-base homeostasis is instable in laparoscopic surgery because of the CO_2 insufflated and the decrease in pulmonary compliance. It is essential to monitor pH levels and $PaCO_2$ in order to keep the patient in normocapnic range and in ideal pH level, as it effects the cardiovascular efficiency and stability. If the patient has a cardiovascular disease the anesthetist should avoid using cardio-depressant drugs. If there is an increase in MAP due to increase in SVR, instead of increasing the concentration of inhalation anesthetics (which may cause myocardial depression, especially in patients with cardiovascular disease) administrating vasodilating agents reducing specifically preload or afterload should be considered[21,28]. However studies report that even in cases which pneumoperitoneum is combined with steep Trendelenburg position (such as RALRP) a deterioration of cardiac function was not present and patients usually tolerate the changes well[3,29]. However, the position and pneumoperitoneum may aggravate mitral deficiency, so it must be kept in mind if a mitral deficiency exists[29]. If a cardiovascular complication is thought to be aggravated or caused by the position or pneumoperitoneum, first IAP should be decreased and if it does not work, CO_2 insufflation should be ceased, gas should be evacuated and position should be reversed to horizontal state. Venous gas embolism is a complication possible to occur during laparoscopic or robotic surgery that may have fatal consequences. It may occur during CO_2 insufflation or during surgical procedure especially if venous structures are involved. During insufflation if the Veress needle is inserted directly into vascular structures results may be much more catastrophic. If the structural integrity of a major vein is disrupted, the risk of gas embolism increases. But it does not have to be a major vein. During transection the dorsal venous complex in RALRP operations subclinical CO_2 gas embolism can be observed as reported in literature[30,31]. The symptoms vary in a wide range; while most of gas embolisms are subclinical and can not be detected by standard monitoring, some might cause catastrophic consequences such as cardiovascular collapse[11,23,30,31]. As it is a life-threatening matter, the anesthetist should be vigilant. In the presence of a gas embolism insufflation should be ceased and the gas should be evacuated immediately. Left lateral decubitus position must be applied to prevent the gas from entering pulmonary artery. A central venous catheter should be placed for aspirating the gas and 100% O_2 hyperventilation and proper cardiopulmonary resuscitation should be applied.

Pulmonary complications

Possible pulmonary complications related to laparoscopy are hypoxemia, hypercarbia, barotrauma, pneumomediastinum, pneumothorax, atelectasis and pulmonary edema[7,12,32]. As it is previously mentioned increased IAP in pneumoperitoneum causes an increase in peak airway pressures, a decrease in lung volumes and a decrease in pulmonary compliance. Trendelenburg position increases these effects further. These changes cause a ventilation/perfusion (V/P) mismatch and atelectasis. Eventually hypoxemia and hypercarbia may occur due to ineffective gas exchange. Hypercarbia and respiratory acidosis may be avoided by hyperventilation, which means 15%-25% increase in minute ventilation should be maintained[12,33]. But during hyperventilation it is suggested to increase the respiratory rate and not the tidal volume; especially in patients with COPD, in patients with history of spontaneous pneumothorax or bullous emphysema; because high peak airway pressures and reduced pulmonary compliance may increase the risk of barotrauma and a spontaneous pneumothorax[33,34]. Increase in minute ventilation may be provided by using both pressure-controlled ventilation and volume-controlled ventilation. Pressure-controlled ventilation was reported to decrease peak airway pressure and increase dynamic compliance and found superior to volume controlled ventilation by Assad *et al*.[35]. But Balick-Weber *et al*.[36] and Choi *et al*.[37] reported that these two ventilation techniques are not superior to each other regarding respiratory mechanics and hemodynamics. Endo-tracheal intubation with either volume or pressure controlled ventilation is the recommended technique, especially for longer operations, because it provides a better control over CO_2 and prevents gastric regurgitation. But for shorter operations which can be performed at lower IAP levels, using conventional laryngeal mask airway (LMA) or a ProSeal® LMA (ProSeal LMA, San Diego, CA, USA) was found to be safe and effective in some laparoscopic gynecological operations and laparoscopic cholecystectomies; therefore it may be valid for laparoscopic urological operations without Trendelenburg position lasting < 2 h and performed at lower IAP levels[38-40]. Increased IAP during CO_2 insufflation and Trendelenburg position may cause the distance between carina and endotracheal tube tip to become shorter leading to inadvertent endobronchial intubation and hypoxemia (due to ineffective ventilation)[41]. Endotracheal tube's position should be checked regularly through the surgery and it should be checked if both sides are equally ventilated in order to avoid this complication. Patients without pulmonary disease usually tolerate side effects of pneumoperitoneum and Trendelenburg position well with proper anesthetic management and postoperative care[23]. However, it may be more severe in patients with pulmonary dysfunction; so these patients must be carefully assessed preoperatively with pulmonary function tests and arterial blood gas analysis should be performed at preoperative evaluation and regularly during surgery through an artery cannula. If hypoxemia and hypercarbia persist even after proper interventions, pneumoperitoneum should be ceased and a slow re-insufflation should be applied or convertion to open surgery should be considered if necessary[12].

Subcutaneous emphysema

Subcutaneous emphysema is the presence of gas in subcutaneous tissue passing through a disruption in peritoneum or through an inadvertent placed trocar. In a study conducted by McAllister *et al*.[42] showed, up to 56 % of the patients after laparoscopic surgery had subcutaneous emphysema. However, this situation is mostly benign and is not serious. The clinical detection rate is between 0.3%-3% in laparoscopic surgeries[7]. Subcutaneous emphysema may extend to mediastinum and pleura causing pneumothorax and pneumomediastinum, or vice versa it may be the sign of an extended pneumothorax or pneumomediastinum to subcutaneous tissue[7]. Most of the cases with subcutaneous emphysema is clinically insignificant, however its relevance with pneumothorax and pneumomediastinum must be remembered. Also, if the neck is involved, obstruction of upper airways may be present. Risk factor for subcutaneous emphysema are multiple trocars, end tidal CO_2 levels higher than 50 mmHg, prolonged operative time and old patients[43].

CO_2 gas reserved by subcutaneous emphysema may cause hypercarbia, so increased ventilation might be necessary to cope with the increased end tidal CO_2 concentrations.

Pneumothorax and pneumomediastinum

There are multiple ways for a pneumothorax to occur during laparoscopic surgery. Either a real pneumothorax may occur due to high airway peak pressures causing a congenital bulla to rupture or insufflated CO_2 may infiltrate thoracic cavity. Insufflated CO_2 may create a capno-thorax or capno-mediastinum (pneumothorax or pneumomediastinum caused by pure CO_2 that has been insufflated) through congenital or acquired (injuries caused by surgery) diaphragmatic defects, as a result of CO_2 dissecting through retroperitoneum or by the extension of subcutaneous emphysema up to pleura or mediastinum[7]. Mostly the cases are asymptomatic and conservative treatment and close observation is sufficient. However increase in peak airway pressures, hypoxemia, hypotension and even cardiac arrest may be present according to the severity of this complication[7,32]. If cardiopulmonary functions are compromised, releasing of pneumoperitoneum and placing a chest tube must be considered. Usually a chest tube insertion is sufficient[44]. However thoracic complications after laparoscopic urologic procedures are rare and most of the cases are subclinical, thus a routine postoperative chest radiography was not found to be necessary[44,45].

Renal complications

Due to high IAP in laparoscopic surgeries renal perfusion and glomerular filtration rate decreases thus causing oliguria[46]. In multiple studies on animals and humans effects of pneumoperitoneum on renal physiology were examined and the reasons, which were found responsible for this complication, are IAP applying direct compression on renal vascular structures, activation of renin-angiotensin-aldosterone, increase of anti-diuretic hormone and low cardiac output[47-49]. To prevent oliguria sufficient hydration of the patient before and during the operation must be provided and urine output must be observed especially in prolonged and major surgeries. Also using low-dose dopamine at 2 mcg/kg/min and nicardipine at 0.5 mcg/kg/min was found useful to protect kidneys from hypoperfusion and renal dysfunction[50,51].

Neurologic complications

As previously discussed neurologic complications may occur due to laparoscopic and robotic surgeries as a reason of increase in ICP, cerebral hypoperfusion or hypoxemia. High risk patients with a previous cerebrovascular disorder should be carefully assessed preoperatively. Near infrared spectroscopy may be used to monitor cerebral oxygen levels. Pneumoperitoneum and Trendelenburg position both increases ICP[13,24,25]. High ICP may cause transient or permanent neurologic deficits such as motor paralysis or paresis. In two case reports transient neurologic deficits including quadriplegia and hemiparesis were reported and both patients had full recovery[52,53].

Ocular complications and edema

Trendelenburg position increases intra-ocular pressure. This may cause temporary or permanent loss in vision. Ischemic optic neuropathy, which is a rare complication, was reported after robotic and laparoscopic radical prostatectomy[54]. Corneal abrasions may occur because of chemosis or exposure keratopathy[55]. Eye patchings and transparent occlusive dressings are recommended to prevent corneal abrasions. Prolonged operations in Trendelenburg position may cause facial, periorbital, conjunctival, pharyngeal and laryngeal edema. Edema of the upper airways might cause serious consequences after extubation. If facial edema or conjunctival edema is observed, there is a chance that laryngeal edema might also exist. Therefore if there is a suspicion of upper airway edema, an endotracheal leak test should be done before extubation[11].

Positional injuries and compartment syndrome

Patient positioning is an important preparation for the operation. Improper positioning may cause nerve injuries and compartment syndrome, furthermore it may compromise cardiopulmonary function[12]. Mills *et al*.[56] investigated positioning injuries associated with robotic surgery in their institution and found that 6.6% of 334 patients had positioning injuries. These injuries resolved at least within 1 month but some persisted beyond 6 months[56]. As well as positional effects caused by prolonged lithotomy and Trendelenburg, use of pneumatic compression stockings, intravenous fluid restriction for improvement of surgical view, hypotension and administration of vasoactive medication compromises the proper perfusion of lower extremity, thus increases the risk of compartment syndrome, especially in the lower extremities[57,58]. Compartment syndrome of the upper extremities is relatively rare in the literature, however it is possible especially if higher amounts of intravenous fluid replacement is present[58]. Galyon *et al*.[58] reported a patient with compartment syndrome in three limbs including both lower extremities and left upper extremity after a robotic cystoprostatectomy which lasted about 6 h, and for treatment fasciotomy was performed to all affected extremities[58]. In order to avoid this serious complication pressure points of the patient must be carefully assessed and materials absorbing the pressure must be placed between the body and operating table. Also repositioning of the extremities every 2 h was found to be beneficial avoiding compartment syndrome[59].

Emergency situations

Due to the positions applied to patients and surgical equipment limiting the access to patients, critical interventions such as cardiopulmonary resuscitation or conversion to open surgery may delay. This may lead to lethal consequences. Life threatening emergencies like cardiopulmonary arrest require immediate attention and intervention. Especially in robotic surgery this may be a critical issue, as before the anesthesiology team could start a resuscitation, robot must be undocked. Simulating this situation and having an emergency plan can improve the time of preparation and intervention. O'Sullivan *et al*.[60] experienced a respiratory complication during a robotic sacrocolpopexy. The patient had a decreased sPO_2 and increased airway pressure, thus an emergency undocking of the robotic arms was required. After this complication they reported that they created an emergency undocking protocol, which indicates the roles of each member of the crew in emergency situations[60]. Also Huser *et al*.[61] reported that proper training with repeating simulations improved the time for resuscitation in simulations. To be able to react to a life-threatening emergency swiftly, having a similar training and an emergency protocol may be useful.

CONCLUSION

Minimal invasive surgery is being increasingly more popular. The application of laparoscopic and robotic surgery is now more common. In urology, laparoscopy and robotic surgery may be applied in various operations including uro-oncological surgery. Minimally invasive surgery provides patients many benefits, however robotic and laparosopic surgery also has a risk of many significant and unique complications related to these procedures. Pneumoperitoneum and specific patient positions such as steep Trendelenburg position have important physiological effects on cardiovascular, pulmonary, ocular, renal and neurological systems which may cause serious complications. In order to detect, manage or prevent these complications properly these physiological effects must be thoroughly comprehended. All personnel in the operating theatre should be prepared to all possible complications related to surgical procedure and anesthesia. With proper interventions, careful monitoring and preventive precautions, these complications may be avoided or at least their impact may be minimized.

DECLARATIONS

Authors' contributions

Conception or design of the work: Özgök A, Arslan ME
Data collection: Arslan ME
Data analysis and interpretation: Özgök A, Arslan ME
Drafting the article: Arslan ME
Critical revision of the article: Özgök A

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Mini-invasive Surgery

Original Article

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Magnetic resonance imaging study of orthotic balloon brace used for the treatment of pectus carinatum

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Abstract

Aim: A compressive orthotic brace is considered the first line therapy for patients with pectus carinatum. We designed a brace made of a non-metallic binder equipped with a balloon which can be insufflated to apply variable compression pressure to chondrogladiolar pectus carinatum. The study aimed to study the effect of this brace on patients with pectus carinatum, dynamic magnetic resonance imaging (MRI) studies were obtained.

Methods: Dynamic chest MRI studies were obtained on pectus carinatum patients fitted with the orthotic balloon brace. Patient's vital signs and oxygen saturations were recorded.

Results: Three pediatric patients were studied with the MRI. The variable pressure balloon brace provides effective compression and correction of the pectus carinatum deformity. The compression of pectus carinatum chest did not result in changes in vital signs or oxygen saturations.

Conclusion: Dynamic MRI studies done on pectus carinatum patients showed that chest wall can be molded to a normal shape when a directional force is properly applied without changes in vital functions.

Keywords: Pectus carinatum, magnetic resonance imaging, chest balloon brace

INTRODUCTION

The treatment of chondrogladiolar pectus carinatum was surgical until a compressive orthotic brace was

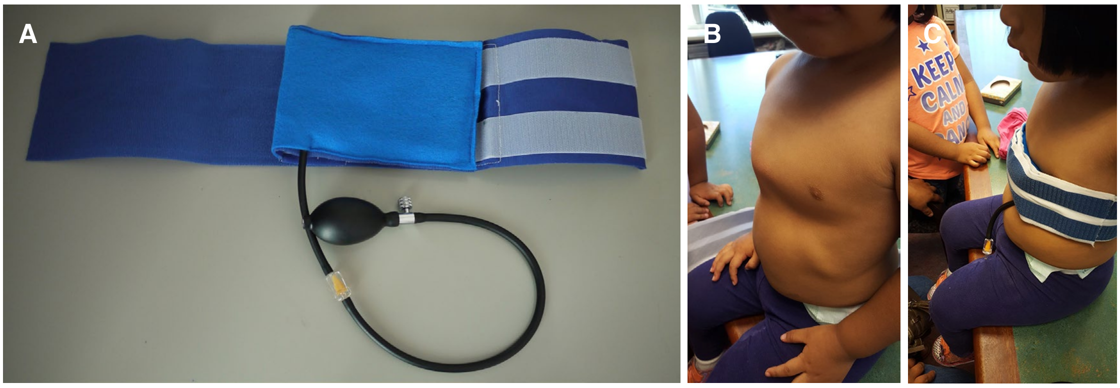

Figure 1. (A) A picture of the balloon brace; (B) a patient with symmetric pectus carinatum; (C) a patient wearing the brace

introduced. Indications for non-surgical therapy include improving cosmesis of the chest and less commonly for chest pain. Operative treatment is used when bracing therapy fails or patient refuses to use a brace for therapy. Non-surgical treatment is based on the malleability of chest to conform to external forces. Vidal *et al.*[1] were the first to report a non-operative approach using a plaster cast followed by a plaster jacket in 1977. The second report was by Haje and Raymundo[2] in 1979 and 1992, who called their design a dynamic chest compressor. Other studies showing the efficacy of compressive orthotic brace and various brace designs have been reported[3-5]. Although the efficacy of various brace designs have been demonstrated, a dynamic radiologic study of pectus carinatum patients wearing a chest orthotic brace has not been reported in the literature. In particular, radiologic demonstration of chest shape alteration and cardiopulmonary response have not been elucidated. Therefore, to better understand the effect of an orthotic balloon brace on patients with pectus carinatum, dynamic magnetic resonance imaging (MRI) studies were obtained and analyzed using a brace that is non-ferromagnetic.

METHODS

A balloon brace is an orthotic device that is composed of a non-stretchable binder with Velcro ends and an inflatable balloon, confined within the pocket of the brace. The brace is wrapped around a patient's chest [Figure 1]. The part of the brace containing the balloon portion is placed against the anterior protruding chest. The balloon is inflated with an insufflation bulb. There is an in-line one way valve, which allows the air to enter the balloon. When the balloon is insufflated, the portion of the chest underlying the balloon is compressed with variable pressure depending on the amount of air insufflated. Sufficient air is insufflated to cause the chest to become flat or to cause the chest to assume the shape of pectus excavatum. The pressure of the air insufflation was not measured since this is dependent on the chest compliance of each patient. The brace has no metal components. The weight of the regular size brace for a teenager weighs 150 g.

Dynamic chest MRI study was performed on three patients with varying amounts of balloon insufflation. Vitals signs and pulse oximetry readings were recorded with and without balloon insufflation while the MRI was obtained.

The chest MRI was obtained using a Philips 1.5T Intera-Achieva MR scanner R3.2.2 (Best, Netherlands). A 4-element phased-array torso was used for the examination. Static, free-breathing, respiratory-triggered single-shot T2-weighted axial and sagittal images were first acquired to visualize the chest anatomy. Then, dynamic (real-time) MRI of the chest centered over the level of the diaphragm was performed in axial and sagittal planes with Steady-State Free Precession sequence with in-plane spatial resolution of 1.4 mm × 1.4 mm and 10 mm thick slices. With optimization of the field-of-view and application of parallel imaging acceleration, the scan time for one slice was between 220-290 ms. This was the temporal resolution of the

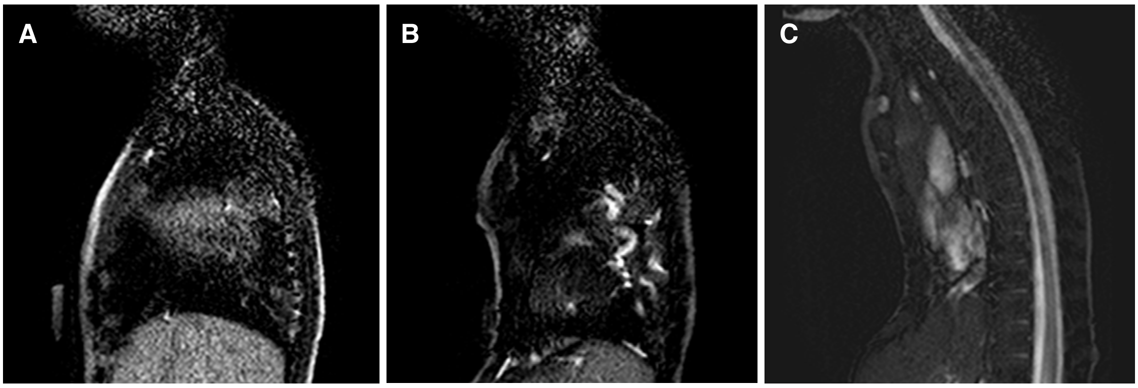

Figure 2. (A) A midline sagittal image from the dynamic magnetic resonance imaging in a patient with pectus carinatum chest is shown before the balloon brace is insufflated; (B) with sufficient insufflation of the balloon, the chest is made flat. This level of correction corresponds to the desired target of chest correction; (C) with extreme insufflation, the pectus carinatum chest can be converted to a pectus excavatum chest

dynamic series of images. A total of 60 images per location were obtained while the patient was freely breathing. A midline sagittal slice and an axial slice centered at the level of maximal AP diameter of the lower chest were acquired with and without balloon compression in place.

Institutional Review Board approval was obtained for the study.

RESULTS

The ages of three patients were 2, 10, and 15 years old. For the 2-year-old patient, sedation with intubation was used. During the study, this patient was allowed to breathe on his own. Older patients did not need intubation. All of them had symmetric pectus carinatum and without cardiopulmonary disease. They were seen by Pulmonology service and underwent pulmonary function test. They were not treated with an orthotic brace prior to the MRI study.

MRI showed preferential depression of the anterior chest wall underlying the balloon. The depression correlated with the amount of air insufflation of the balloon. The chest can be effectively made flat with the balloon brace [Figure 2]. When the chest was made flat, there was transient depression in oxygen saturation upon balloon insufflation followed by rapid normalization without external intervention. The oxygen saturations before balloon insufflation ranged between 96% to 98%. After balloon insufflation, there was desaturation down to range 92% to 94%. No changes in blood pressures and respiratory rate were noted. When the balloon pressure caused the chest to assume a shape of pectus excavatum persistent oxygen desaturation down to 90% was observed. Upon lowering the balloon pressure to cause the chest to be flat again, vital signs and oxygen saturation as indicated by pulse oximetry returned to the same values as without insufflation in all patients.

DISCUSSION

The basic design of chest orthotic braces consists of plates in the front and back of a patient's chest. These are connected by metal struts or straps that are tightened to apply anterior to posterior force on a chest. Although the efficacy of such a design to correct pectus carinatum has been shown in multiple studies[3-5], there has not been any dynamic study that examined the internal effects on the chest viscera from a brace compression. This dynamic MRI study showed that preferential compression of anterior chest did not alter blood pressure, pulse, or pulmonary function. The finding indicates that the patient's cardiac and pulmonary function can compensate for the compression. The chest wall area under the balloon is clearly observed to be depressed, and the level of depression is a function of the amount of air insufflation in the balloon. It was also noted the width of the chest increased as the anterior to posterior chest wall distance decreased from compression. This is an expected result since the circumference of the chest will distribute laterally as the forced is applied from front to the back of the chest. Since the binder conforms to the shape of the chest, the lateral displacement of the chest is not hindered.

The criteria for using a compressive orthotic brace on patients with pectus carinatum are two-fold: patient is willing to wear the brace for at least 8 h a day, and patient wants to improve the chest cosmesis. If the chest is extremely stiff, in particular for older patient, the force of initial correction may be too high to compress the chest. For these patients, the failure rate for brace compression therapy is high. For patients who have a very hard "knuckled" carinatum, brace therapy may not work since the force needed to compress the knuckle is too high. An excision in this case would be preferred. Index of severity for pectus carinatum is not well established unlike the index used for pectus excavatum. The most common index of severity used for pectus excavatum is the Haller index. The Haller index concept can be applied to pectus carinatum but it is not often used as an index to describe pectus carinatum. Due to the absence of optimal index for pectus carinatum, the severity of the pectus carinatum is usually defined as mild, moderate or severe. This is a subjective index. A better index for pectus carinatum is needed. Compressive orthotic brace can be tried on all patients of severity. The effectiveness is largely dependent on compliance, and the length of therapy is dependent on the severity of the condition. Mild condition will take short time to fix with good compliance, within 3 months. For moderate condition, it may take 6 months or longer. For severe conditions, it may take one year or longer.

The weaknesses of this study include the small number of participants in this initial cohort. Based on this limited MRI results, we have started to apply the balloon brace on our patients. We encourage our patients to use the brace at least 12 h a day or use the brace as much as they can. They should also use the brace during sleep. They may remove the brace during vigorous exercise such as during Physical Education at school. Our preliminary results on 30 patients treated thus far showed no complications such as skin ulceration. This finding is consistent with the design of the balloon brace. The contact surface of the balloon brace conforms to the surface shape of the chest and provides even force distribution compared to a hard surfaced non-malleable orthotic devices typically available in the market.

In summary, dynamic MRI studies done on pectus carinatum patients wearing an orthotic chest brace show chest wall can be molded to a different desired shape when a directional force is properly applied.

DECLARATIONS

Authors' contributions

Manuscript preparation: Ewbank C, Idowu O, Chung T, Kim S
Data analysis: Idowu O, Kim S, Chung T
Literature search: Ewbank C, Kim S
Data acquisition: Idowu O, Kim S, Chung T
Study design and definition of intellectual content: Idowu O, Kim S

Data source and availability

All data are stored in a password protected hard drive and available on request via the corresponding author.

Financial support and sponsorship

None.

Conflicts of interest

The authors have no conflicts of interests or financial disclosures.

Patient consent

Patient consents were obtained for the study and publication.

Ethics approval

Institutional Review Board approval was obtained for the study.

Copyright

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Mini-invasive Surgery

Original Article

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Laparoscopic transgastric resection of gastric submucosal tumor located near the esophagogastric junction

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Abstract

Aim: Laparoscopic wedge resection is widely accepted as the choice of treatment for gastric submucosal tumors (GST). However, tumors on the posterior wall at the esophagogastric junction (EGJ) are difficult to approach. Laparoscopic transgastric resection (LTR) is a novel technique to remove gastric tumors that are unresectable by endoscopy due to their size and location. The aim of the article is to assess the feasibility and oncological outcomes of this laparoscopic approach for intraluminal GST located in the posterior wall and near the EGJ.

Methods: A retrospective analysis of all patients with GST located at the EGJ who underwent LTR at our institution from January 2015 to February 2016 was performed.

Results: Of the 4 patients who underwent LTR, 3 were female and 1 was male, with a mean age of 74.5 years. LTR was successfully performed in all the cases. All patients received a complete resection with negative margins. Histopathologic diagnoses were gastrointestinal stromal tumor in 2 cases and leiomyoma in the other 2. Median tumor size was 3.45 cm. The mean operation time was 173 min (range 120-232 min). One patient experienced a postoperative hematemesis, but was treated conservatively. The mean postoperative stay was 8 days (range 4-15 days).

Conclusions: LTR is feasible and difficult localizations can be reached with ease. It is an appropriate alternative to laparoscopic wedge resections especially for localizations that cannot be accessed by laparoscopy such as tumors located near the EGJ.

Keywords: Gastrointestinal stromal tumors, esophagogastric junction, transgastric resection, laparoscopy, gastric submucosal tumors, laparoscopic

INTRODUCTION

Gastric submucosal tumors (GST) are rare, accounting for < 1% of gastrointestinal tumors. Currently, surgical resection remains the only chance for cure[1].

Laparoscopic wedge resection is widely accepted as a choice of treatment for GST especially for tumors in the anterior wall, lesser curvature, and greater curvature. However, the difficulty in accessing tumors located in the posterior wall and esophagogastric junction (EGJ) requires alternative approaches[1].

Laparoscopic transgastric resection (LTR) is a novel technique of removing gastric tumors that are unresectable by endoscopy due to their size and location. However, there are limited reports on this technique as this clinical entity occurs rarely[1-5].

The aim of the article is to assess feasibility and oncological outcomes of the laparoscopic approach for intraluminal GST located in the posterior wall and near the EGJ.

METHODS

A retrospective analysis of all patients with GST located at the EGJ underwent LTR at our institution from January 2015 to February 2016 was performed.

Patient demographics, preoperative symptoms, imaging studies, operative data, complications, hospital stay, and follow-up were analyzed.

Preoperative, postoperative and long-term clinical assessment

All the patients underwent a standard preoperative workup including physical examination, blood analysis, chest X-ray, upper gastrointestinal barium meal X-ray study, oral endoscopy, eco-endoscopy and computerized tomography scan [Figure 1].

Postoperatively, patients were placed on a clear liquid diet and discharged home on a soft diet. Follow-up was performed approximately 1, 2, 4 weeks, the 6th and 12th months, then every year after surgery where an oral endoscopy was performed.

Histopathologic diagnoses were gastrointestinal stromal tumor (GIST) in 2 cases and leiomyoma in the other 2. Median tumor size was 3.45 cm (range 2.3-5.5 cm).

Patient's position and trocar's placement

The surgery was performed with the patient under general anesthesia and placed in a modified lithotomy position. The surgeon stood between the patient's legs with the camera surgeon on the patient's right side and the assistant on the left.

A four-port technique was employed in the upper abdomen: epigastric 5-mm ballon trocar, left midclavicular 10-mm ballon trocar, left hipocondrium 12-mm ballon trocar and supraumbilical 10-mm trocar (Applied Medical). Nathanson liver retractor was used in selected cases when the upper part of stomach was covered with bulky liver [Figure 2].

Gastric wall incision and intragastric trocar insertion

Pneumoperitoneum was created with Veress needle in left upper hypocondrium and carbon dioxide was insufflated to maintain the intra-abdominal pressure at 10-12 mmHg. A 30º-degree laparoscope was used.

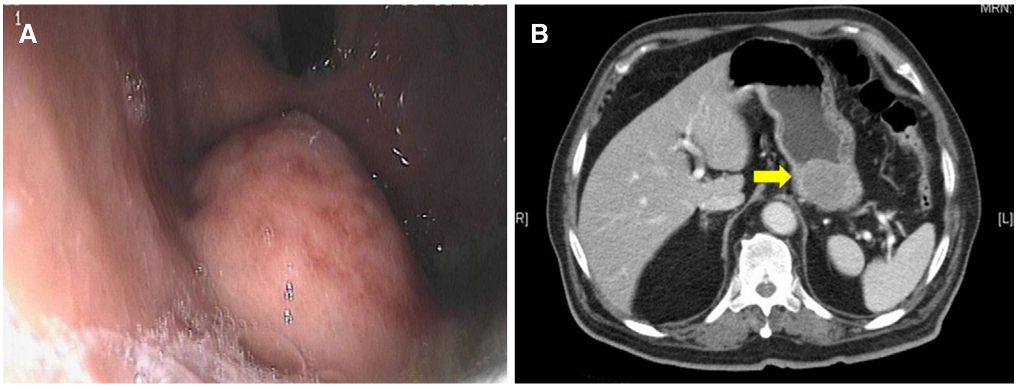

Figure 1. Gastrointestinal stromal tumor near the esophagogastric junction observed in oral endoscopy (A) and computerized tomography scan (B)

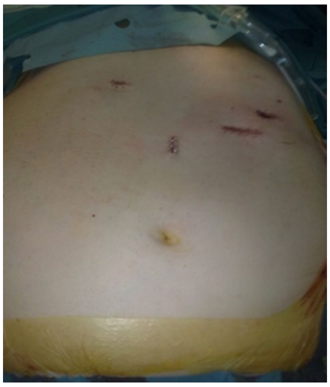

Figure 2. Trocar placement

First, we started the procedure after inserting a supraumbilical 10-mm port. A second 10-mm ballon trocar was placed along the left midclavicular line and a third port, sized 5-mm ballon trocar was placed along the epigastric line, under direct vision.

The procedure started with the incision of a suitable point on the gastric wall, which served for the introduction of a 12-mm balloon trocar. This step was performed using the Ultracision [Figure 3A]. This trocar was used to allow the introduction of a 10-mm scope and also to allow the sealing of the stomach to the abdominal wall. The other 10 and 5 mm balloon trocars were inserted into the stomach [Figure 3B].

Tumor resection

Once balloon trocars were inside stomach, pneumogastrum was established (4-6 mmHg).The location of the tumor was confirmed after the introduction of the scope [Figure 4A]. For tumors near the EGJ, precaution was taken not to involve the EGJ itself. For that, the EGJ needed to be clearly identified either by insertion of the tip of a nasogastric tube or a gastroscope. To facilitate the resection, sometimes we used a tractive suture into the tumor. The resection was performed by means of the Ultracision (Harmonic Scalpel; Ethicon Endo-Surgery, Cincinnati, OH, USA), making sure to leave a 1-cm of clear tissue around the lesion without breach of the capsule [Figure 4B]. Once the tumor has been removed, we introduced an Endobag, and retrieved the specimen through the ballon trocar.

Closure of the gastric defect

A single layer of interrupted sutures with non-absorbable material (Ethibond 2/0) was used to closure the posterior gastric wall [Figure 5]. The trocar was then be retrieved under vision and the anterior gastric wall sutured with interrupted Ethibond 2/0 suture. A methylene blue test was performed in order to exclude gastric leaks.

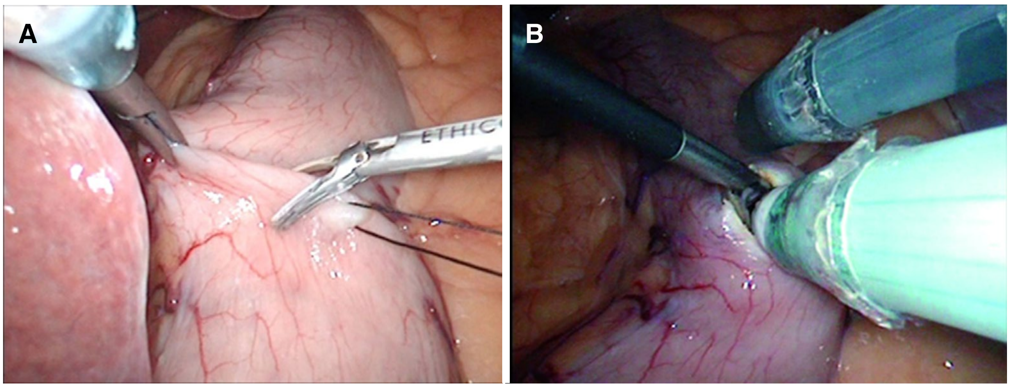

Figure 3. (A) Suitable point on the gastric wall. Open of stomach; (B) introduction of balloon trocar inside stomach

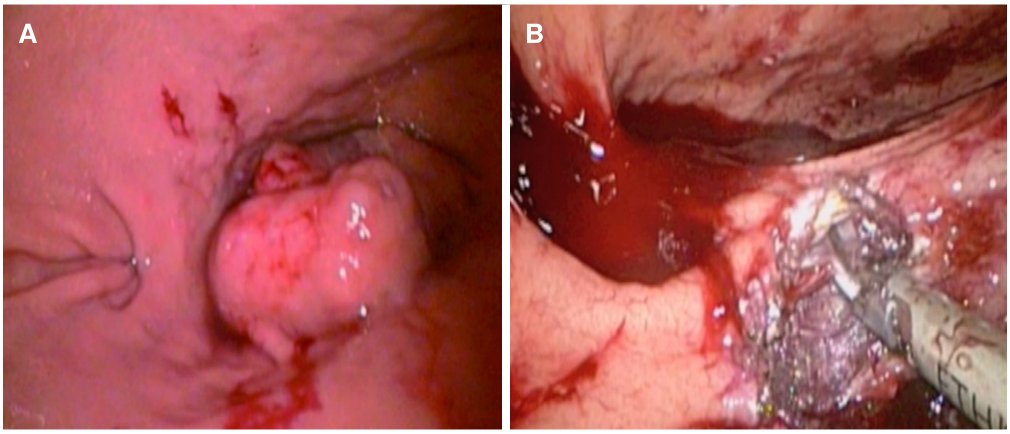

Figure 4. (A) Submucosal stromal tumor near the esophagogastric junction; (B) resection of gastric submucosal tumor with Ultracision

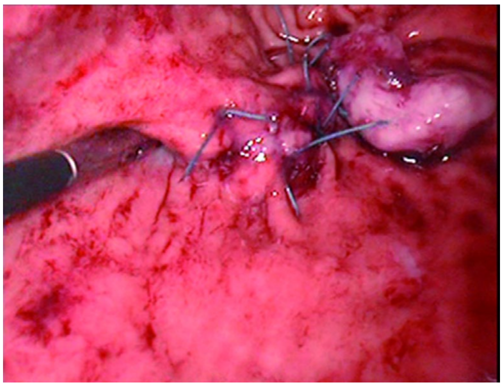

Figure 5. Closure of the defect

No drains were normally used but a nasogastric tube was maintained overnight.

RESULTS

Of the 4 patients who underwent LTR, 3 were female and 1 was male, with a mean age of 74.5 years (range 64-82 years). Demographics and tumor characteristics were described in Table 1.

LTR was successfully performed on all the cases. All patients received complete resection with a negative margin.

Table 1. Demographic characteristics of patients

	Case 1	Case 2	Case 3	Case 4
Age (year)/gender	82/M	74/F	78/F	64/F
ASA	III	II	II	III
Comorbidities	COPD, DM	Hypertension	Hypertension, DM, DL	Hypertension, dilated myocardiopathy, ischemic cerebrovascular accident
Symptoms	Haematemesis	Haematemesis	Epigastric pain	Epigastric pain
Diagnosis	Endoscopy, CT scan	Endoscopy, Eco-endoscopy, CT scan	Endoscopy, Eco-endoscopy, CT scan, Barium swallow MRI	Endoscopy, Eco-endoscopy, CT scan
Hystopathology	GIST low malignancy, mitotic index < 5/50	GIST low malignancy, mitotic index < 5/50	Leiomyoma	Leiomyoma
Size tumor (cm)	5.5	3	3	2.3
Operative time (min)	120	195	145	232
Intraoperative complications	None	None	None	Methilene blue leakage
Postoperative complications	None	None	None	Fever, haematemesis
Oral intake (days)	3	2	3	10
Hospital stay (days)	7	4	6	15
Mortality	No	No	No	No

M: male; F: female; ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CT: computerized tomography; GIST: gastrointestinal stromal tumors; DL: dyslipemia; MRI: magnetic resonance imaging

The mean operation time was 173 min (range 120-232 min). There were no conversions. There were no intraoperative complications, but in one of the patients, a methylene blue leakage was observed when suture was checked, which was reinforced. No postoperative complications were described, but patient with methylene blue leakage experimented hyperpyrexia in the first 24 h after operation and haematemesis. Both problems were treated conservatively.

The mean postoperative stay was 8 days (range 4-15 days). There was no death in our series.

At a mean follow-up of 31 months, all of our patients are asymptomatic and free of recurrence. None showed evidence of stenosis of the EGJ or acid reflux symptoms.

DISCUSSION

Laparoscopic wedge resection is widely accepted as a choice of treatment for GST, especially for tumors in the anterior wall, lesser curvature, and greater curvature. However, tumors on the posterior wall at the EGJ remain difficult to approach[1-5].

Privette *et al*.[6] proposed a tailored location-based standardized approach to resection of gastric GIST. This new classification on the basis of tumor location considers type 1 tumors located in fundus and greater curvature, type 2 for tumors in the antrum-prepyloric region and type 3 for tumors in the lesser curvature and EGJ. The surgical approach as dictated by tumor location would be a laparoscopic wedge resection for type 1, a laparoscopic distal gastrectomy for large type 2 tumors, and a laparoscopic transgastric resection for type 3.

The optimal approach to GISTs located near EGJ is not well defined. Such tumors have been reported as the reason for conversion, planned open procedure, and exclusion indication for laparoscopic approach[7].

Several laparoscopic approaches have been described for the surgical treatment of gastric GIST near the

EGJ or posterior wall. These approaches include tumor enucleation, exogastric wedge resection, transgastric tumor-everting resection, intragastric tumor everting resection, laparoscopic and endoscopic cooperative surgery and esophagogastrectomy[8-11].

Laparoscopic transgastric resection of GST was first described by Geis *et al.*[12]. Several publications of this technique have shown the procedure to be feasible and safe with good outcomes in the resection of GISTs located near EGJ, posterior wall and the antropyloric region[1-5]. However, certain principles need to be practiced when performing this intervention.

First, this procedure requires greater expertise and laparoscopic skills, so whether you want to follow strict oncological outcomes, this surgery should be only performed in hands of experienced surgeons with advanced laparoscopic skills.

In our experience, we advise the use of ballon trocars in order to minimize the leakage of pneumogastrum during the resection of the tumor. Moreover, we consider trocar placement as the key of a successfully resection. In fact, before introducing any trocar, when the upper part of stomach is covered by bulky liver,we first introduce a Nathanson liver retractor in order to define the anatomy. It is important to put the trocars as high as possible, and to introduce the left balloon trocar in the midline of the epigastrium in order to reduce the distance between the abdominal and gastric wall.

We have not used any system of occlusion of duodenum to maintain air-inflated stomach, and we have not had any problem during resection of the tumors.

Another important step is avoiding EGJ stenosis, especially when an endoscopic linear stapler is used to remove the specimen. In addition, one needs to confirm if the EGJ is intact prior to firing, either with the position of a nasogastric tube or a gastroscope.

Most authors utilized the technique of transgastric stapled resection as it allows simultaneous resection and closure of the defect in the stomach. In our series, we have preferred the use of ultrasonic device to remove the tumor because it is feasible to manipulate and to avoid bleeding. With the stapling, overall operating time would be shortened, because it was not require closing the gastric wall with suture. Finally, we have only had one intraoperative complication using this technique. In one patient, a methylene blue leakage was observed when the suture line was checked, requiring reinforced.

Caution need to be taken to minimize tumor handling in order to prevent tumor rupture or spillage. It is advisable to avoid grasping the center of the tumor, but instead to grasp the normal mucosal surrounding it. For this reason and also to facilitate the resection, sometimes we use a suture into the tumor for retraction.

Moreover, it is important to achieve good haemostasis during the surgery, avoiding using suction and irrigation in order to maintain air-inflated in the stomach.

In conclusion, and if these principles are followed, laparoscopic transgastric resection seems to be a safe and effective procedure for gastric submucosal tumors located near the esophagogastric junction. However, advancedtraining in laparoscopic surgery is advised.

DECLARATIONS

Authors' contributions

Study conception and design, drafting of manuscript: Priego P
Data collection: Cuadrado M, García-Moreno F
Analysis and interpretation of results, critical revision: Carda P, Galindo J

Financial support and sponsorship
None.

Data source and availability
All data are stored in the computer lab of Department of General Surgery at Ramon y Cajal University Hospital.

Conflicts of interest
There are no conflicts of interest.

Patient consent
Informed consent was obtained from all patients for being included in the study.

Ethics approval
Study was approved by Local Ethics Committee.

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Mini-invasive Surgery

Review

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Robotic urologic surgery complications

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Abstract
Robot-assisted surgery is a commonly performed procedure in the recent urological approach. The scientific data that reveal the complication rates also tend to increase by the rising popularity of the robot-assisted surgeries in the treatment of urological cancers. Patient characteristics, nature of the cancer and learning curve of the surgeon are the determinant factors of the complication rates. Nevertheless, robot-assisted surgical techniques are safer with acceptable morbidity and mortality rates as compared to open surgical methods. In urology practice, robotic surgery is most commonly performed in the treatment of prostate cancer. Thus, this review subjected to reveal the commonly seen and the serious complications of robot-assisted radical prostatectomy, and their prevention and management.

Keywords: Urology, robot-assisted surgery, prostatectomy, complication

INTRODUCTION

Robot-assisted surgery is a minimally invasive procedure with a rising popularity worldwide. In urology practice, robotic surgery is most commonly performed in treatment of prostate cancer (PCa). As the relatively high morbidity and mortality rates of open radical prostatectomy (ORP) are considered, robotic surgery becomes the preferred method in the treatment of PCa with distinct advantages in comparison with open surgery in terms of functional and oncologic outcomes and complication rates.

The complication rates are reported following ORP by many authors. However, uniformity does not exist in data documentation and reporting methods of the complications resulting in incomplete data collection and problematic comparisons among different surgical approaches and different institutional series.

Clavien-Dindo classification has been used as a standardized classification in general surgical literature[1]. Martin *et al.*[2] proposed a report in 2002, to standardize the classification criteria that should be incorporated into surgical complication reports including definitions of general and procedure-specific complications, data accrual, and follow-up period, inclusion of length of stay and outpatient information, identification of mortality and morbidity rates, application of a grading system for complications, and analysis of risk stratification. However, they reported hepatectomy, pancreatectomy, and esophagectomy as specific examples[2]. Donat[3] modified these criteria in 2007, to include procedure-specific complications concerning urology such as inadvertent visceral injury, bleeding and transfusion rates, urine leakage, and lymphocele formation.

This paper aimed to present the commonly seen and serious surgical complications of robot-assisted radical prostatectomy (RARP) as the most frequently performed robot-assisted procedure in urology practice, and their prevention and management.

METHODS

A systematic search was performed in PubMed database. Studies that referred to RARP complications are detected and evaluated. Papers were identified through database screening and after initial screening. Only the full text available articles in English, published between 2000 and 2017 were included. The keywords comprised "urology, robot-assisted surgery, prostatectomy, complication". Most commonly seen robot-assisted surgery complications and radical prostatectomy complications were individually researched. As the result, an overview of most commonly seen RARP-related complication topics that should be useful in robotic urology.

RARP COMPLICATIONS

The number of robot-assisted procedures increases gradually in urology practice. In USA, 67% of prostatectomies have been performed robotically[4]. Even though, open radical cystectomy has higher complication rates compared to RARP[5], a great number of surgeons have been in their learning curve in terms of robotic urologic surgery practice thus may explain the most of the robotic surgery complications.

Rectum and bowel injuries

Rectal injury is a rare but devastating complication of RARP. In a recent systematic review and meta-analysis, the incidence of rectal injury was reported as low as 0.2%[6]. Patient history of prostate or rectal surgery, hormonal therapy, radiotherapy, periprostatic fibrosis and infection constitute the risk factors for rectal injury. Besides, the ill-defined plane between the rectum and prostate, and the difficulty in dissection of locally advanced tumors also may be responsible for rectal injuries[7,8].

Novara *et al.*[9] analyzed 415 clinically localized PCa patients who underwent RARP. Five cases were complicated with rectal injury, and all of them were detected intra-operatively (1.5%). The lesions were sutured the lesions immediately in 2 or 3 planes, and patients used broad-spectrum antibiotics for 7 days and took liquid diet for 4 days. The bladder catheter was removed after a median of 9 days. The postoperative course was uneventful for all cases[9].

Wedmid *et al.*[10] reported 11 rectal injury cases out of a totally 6650 RARP patients. Rectal injury was recognized in 8 of 11 patients intra-operatively and repaired in the same session. Primary repair was performed in 7 cases by the robotic surgeon. Diverting colostomy with primary repair was performed in only 1 patient. Two and three-layer closure was applied for the full thickness lacerations[10].

Hung *et al*.[11] detected the bowel injury rate as 1.04% in total 288 RARP patients. Before the RARP, all of the patients were received transurethral resection of the prostate. Rectal injury was detected in 2 cases and sigmoid colon in 1. Sigmoid colon injury was unrecognized during the course of RARP and therefore could not be repaired intra-operatively. Peritonitis leading to bowel resection and colostomy was the warning symptom in this case. In 1 patient with rectal injury, late recto-urethral fistula was detected. Colostomy, prolonged urethral catheterization, and perineal repair were performed, and colostomy was taken down subsequently after recovery.

Ileo-colonic injuries primarily present postoperatively with abdominal distention, ileus and absent peritoneal signs. Nowadays, primary repair is preferred without colostomy in most cases. Typically 2-layer closure with 2/0 polyglactin is used for repair and the compliance of sutures are tested by air insufflation through the rectum. Prolonged catheterization is recommended for a mean of 14 days. Failure to recognize and immediately treat a bowel injury may result in a high mortality rate up to 3% and high morbidity[12]. However, careful and sharp dissection by the assistance to hold the rectum posteriorly with a suction irrigation tip, and avoiding entry into the perirectal fat prevent rectal injury in RARP[11].

Urine leakage

Urine leakage is a prevalent and low-grade surgical complication with the rate of 1.8%[6]. Increased drain output is the most common sign. Drain creatinine level is used to detect the type of the fluid.

Jacobsen *et al*.[13] reported the rate of the urinary leakage as 2.1% in their study including 236 RARP patients. Age, smoking, diabetes mellitus, hypertension and prostate volume were not found to be associated with anastomotic leakage. However, obesity and excessive bleeding were associated with decreased visibility of the bladder neck, hampering suture placement in urethro-vesical anastomosis[14]. As a surgical factor, non-eversion of the mucosa was suggested for tighter anastomosis instead of eversion[15].

The origin of urine leakage may also be the ureteral injury as well as the urethro-vesical anastomosis. Urgent management is needed in urethral injury. Cystography should be used to detect the origin of the leakage. Prolonged catheterization is recommended for a mean of 10 to 14 days. Cystography should be repeated in case of high volume leakage. If the leakage is observed as minimal, catheter should be removed one week later with no need for cystography[16,17].

Uroperitoneum is the most serious short-term complication of the urine leakage, and may lead to peritonitis, deterioration in renal functions and ileus. Before the reoperation decision, pelvic drain or nephrostomy tube can be placed[14].

Ureteric injuries

Most of the ureteric injuries can be detected in postoperative period. The incidence varies between 0.1% and 0.3% during RARP[18]. The injury may be at several different levels of the ureter. The distal ureter injury risk increases while performing Montsouris approach[19]. In patients with transurethral resection of the prostate (TUR-P) history, the ureteral orifice may not be in its typical location. Attention must be at the highest level to avoid cutting closely to the ureteral orifices during the dorsal dissection of the bladder, especially in post-TUR-P cases.

The ureter can be mistaken in an extremely lateral dissection to find vas deferens, and therefore may be ligated, transected or injured thermally. In prevention, tubular structures as the vas deferens must be divided after being sure of its exact identity. Vas deferens converges in the midline from lateral to medial in differentiation from ureter.

Medial ureteral injury usually occurs during the extended pelvic lymph node dissection (PLND) at the level of the iliac vessels. Ureters should be visualized clearly to avoid any type of injury. The safety distance increases by pulling the ureter away with the help of robotic arms.

Any type of ureteral injury can be corrected during the course of robotic surgery. In non-transecting injuries, ureteral stent should be placed through the bladder opening. Repair with 5/0 Monocryl (Ethicon) suture after stent placement allows the correction of partially or fully transected ureters. Transverse closure of longitudinal defects prevents narrowing of the ureter. In case of wide injury in the ureter or ureteral orifice, ureteral reimplantation may the treatment choice[20].

Bleeding

Postoperative bleeding rate was reported as 0.5%-2.0% according to various definitions after radical prostatectomy. Most papers reported blood loss between 100 and 300 mL[21-26].

It is possible to cope with the bleeding that occurs during the operation. However, bleeds that are not seen due to the increased intra-abdominal pressure may cause bleeding afterwards. Bleeding is most often seen at the dorsal vein complex, lateral pedicles and port sites. Therefore, the intra-abdominal pressure should be reduced after the operation even if it is expected to decrease for a while, and then the hemostasis should be repeated. After the ports are removed, it should be checked whether any bleeds exist arising from the port sites.

In a case report, Lorenzo *et al.*[27] reported a small perforation at iliac vein during their PLND performance, and they denoted that bleeding was stopped by the bipolar forceps and 5 mm metal clipping.

In a study consisted of 1000 RARP patients, Ahmed e*t al.*[28] reported that blood transfusion was needed for 15 (1.5%) patients for approximately 4.4 units per patient. The transfusion indication was based on tachycardia and hypotension except 6 patients who needed transfusion due to significant cardiac disease history to maintain hematocrit level > 30%[28].

Patel *et al.*[29] indicated complication rates as 4.3% in a series of 1500 patients including 8 hemorrhages, 5 of which required blood transfusion due to decrease in hemoglobin levels at postoperative 5th hour. Bleeding stopped at post-operative 3rd-4th days and hemoglobin levels stabilized. All patients were treated successfully without surgical exploration[29]. Controversy, Murphy *et al.*[30] reported complication rates as high as 15.7% in their 400 patient series in which 1 of the 15 complicated cases (3.75% of total) were re-operated due to bleeding.

Postoperative hematomas may also be seen but often resolve spontaneously. Fischer *et al.*[31] also reported urinary retention due to retrovesical hematoma as a rarely observed complication that resolved spontaneously.

Tasci *et al.*[32] reported a total of 5 postoperative transfusion-requiring bleedings among their 317 patient series of RARP. In postoperative 5th hour, hemoglobin levels were found as reduced in these 5 cases. However, vital findings and general status were stable. Subsequent hemoglobin and hematocrit levels continued to fall. Blood and the blood products were transfused. In postoperative 2nd day, ecchymosis was detected on posterior and lateral walls of abdomen, scrotum, and spread up to the legs. Hemorrhage was minimal in abdomen drainage and no bleeding was detected in the abdomen in computed tomography during the follow-up period. However, there was severe hemorrhage sourcing from abdominal walls. Nevertheless, bleeding stopped on the 3rd or 4th day without surgical exploration, and hemoglobin became stable[32].

RARP has extremely low complication rates in terms of postoperative bleeding. This success may be the result of elevated intra-abdominal pressure by CO_2 insufflation, excellent vision quality and thin dissection opportunities.

Veress needle injuries

In Veress technique, the needle should be placed at the horizontal plane at a 45° angle for umbilical access. In obese patients, the needle should be placed at 45° to 90° angle to prevent vascular injury.

A meta-analysis revealed that vascular injury might be seen at a mean rate of 0.044% during laparoscopic access[33]. In management of the vascular injuries related with the Veress needle, we should target to the specific situation. If a nonexpanding small hematoma exists, it may be outlined by clips and monitored during the course of the surgery. If the hematoma is found as expanded in reinspection at the end of the surgery, the hematoma should be opened to explore the bleeding site.

Trocar injury

The major vascular injury incidence related with Veress needles and trocars is approximately 0.1%. A study carried out by US Food and Drug Administration reported totally 32 deaths out of 629 trocar injuries, from 1993 to 1996. Of the deaths, 81% of the deaths were due to the major vascular injuries and the remaining 19% were the result of bowel injuries.

Most of the trocar injuries are nonfatal vascular injuries followed by nonfatal visceral injuries emerging as bowel or abdominal wall hematomas[34]. Among the vascular injuries, the most commonly injured vessels are the aorta, inferior vena cava, iliac vessels and epigastric vessels (due to lateral trocars)[35,36].

In RARP, vascular injuries most frequently occur during the trocar insertion and lymphadenectomy[37]. They can also occur during neurovascular bundle dissection, and during the handling of the dorsal vein complex or the lateral pedicles. Bipolar coagulation and clipping are very effective to control bleeding. If the bleeding persists, the vessel should be tied with straight needle suturing through the abdominal wall[38].

During lymphadenectomy, direct contact should be avoided between the energy-based instruments and vessels. Some reports exist about the failure of the insulation of laparoscopic instruments that results in burning by the direct electrocautery electricity passage through the vessels[27]. A direct cut to the iliac vessels may also occur. Compression is the first step of the treatment. Then pneumoperitoneum should be increased to 20 mmHg. In venous injuries, this action would stop the bleeding and allow repair. In arterial bleedings, rolled gauze sponges should be utilized as a tamponade to stop the bleeding[39].

Patient positioning and compartment syndrome

Patient positioning

Proper patient positioning has a critical role in any surgical procedure. It is necessary for adequate exposure and access, and also reduces the iatrogenic injuries as compartment syndrome and peripheral nerve damage.

Intraoperative physiologic changes include increased intraocular pressure, central venous pressure, intracranial and pulmonary venous pressure, and decreased functional residual capacity and pulmonary compliance. Lung functions may be compromised prominently if the patient is too tightly taped to the table[40]. Prolonged Trendelenburg position may result in pooling of the venous blood in upper extremities. Subsequently, head and neck edema may be seen and also re-intubation may be required due to laryngeal edema and posterior ischemic optic neuropathy (PION) even after minimally invasive radical prostatectomy[41,42]. Orbital stretching or direct compression from facedown prone positioning may also cause permanent vision loss.

The absolute mechanism of PION is unknown, but might be the result of optic nerve ischemia. Multiple factors have been proposed as underlying mechanisms of PION but the PION cases after open radical prostatectomy is found to be associated with prolonged hypotension as the result of excessive blood loss[43,44]. Urologists should immediately consult such patients to ophthalmologists.

Secondary corneal abrasions may be seen due to positional eye edema related with Trendelenburg positioning. Foam-based safety goggles should be placed over the patient's eyes before the operation and should stay throughout 90 min postoperatively in the recovery room, until the patient is oriented enough not to rub his eyes. The use of these goggles presents significant decrease in corneal abrasion rates[45].

Shoulder braces are used commonly to prevent cephalad migration but may lead to brachial plexus injuries if apply excessive pressure on the upper roots and trunks of the brachial plexus[46].

The surgeon should be cautious about the potential for trauma during the docking of the robot and set the arms to minimize the risk. Besides, increased surgeon comfort may protract the operative time, thus increase the risk of neuropraxia and compartment syndrome[41,42].

Compartment syndrome

Lower limb compartment syndrome (LLCS) is a serious complication occurs in RARP but its incidence is low. In a multicenter study, LLCS was developed at 9 cases with the incidence of 0.29%. The prevalent factors were console time > 4 h in 8 cases, to be at early steps of learning curve (less than 20 cases) in 3 cases, obesity (body mass index > 30 kg/m^2) in 5 cases, peripheral vascular disease in 2/9 cases and incorrect positioning in 1 case. Fasciotomy was required in 7 cases, and primarily closed at 5 patients. However, 2 patients required graft to cover the skin defect and were treated with intravenous (i.v.) fluids and analgesia. No amputations and/or deaths were reported.

Correct positioning of the patient is essential to prevent LLCS. Legs should be replaced to the appropriate position just after the robot undocked. Decompressive fasciotomy outcomes become poorer by the time passing. Urologist should be cautious about patients with leg pain in recovery period and early refer the suspected cases to a specialist. During the learning curve, careful case selection and active mentorship is recommended to keep console time < 4 h[47].

Obturator nerve injury

Obturator nerve injury (ONI) is a rarely seen complication of RARP. Besides, the most common nerve injury during RARP is the obturator nerve injury with 0.4% frequency[48,49]. The injury may be in the form of stretching, entrapment by clips, transection or burning of the nerve during PLND. Even though ONI is rare, it is essential to take precaution and recognize promptly for immediate repair to avoid the significant morbidities such as loss of motor and sensory adductor functions. A full knowledge of pelvic anatomy and careful dissection are essential for both prevention and repair of the ONI.

In prevention, optimal visualization of the nerve should be provided. Obturator lymph nodes should be pulled medially for observation of the nerve. Clips must be placed carefully and parallel to the nerve. To prevent electrofulguration effects, we should better prefer bipolar cautery. In case of a total transection, if recognized during the RARP procedure, the transected nerve edges should be sutured to prevent persistant disfunction and ensuing atrophy of the adductor muscles[50].

Ghazi *et al*.[51] reported their complication rates as 3 of total 1503 RARP cases in terms of ONI. Inadvertent clipping was hold responsible for the complication. They recognized and removed the clips intra-operatively and they observed the patients postoperatively.

Gözen *et al.*[52] reported 2 cases with obturator nerve transection in their total 1027 RARP cases. All injuries were detected at the proximal part of the obturator nerve. They recognized the both cases during the RARP and immediately removed the clips by dissectors. They repaired the transected nerve edges with 6/0 polypropylene suture. One of the ONI cases needed to administer a neurotropic drug, and the other one also received physiotherapy besides the neurotropic drug. In a mean follow-up period of 19 months, they observed a successful recovery in the both cases[52].

Lymphocele

A lymphocele is lymphatic fluid collection as a consequence of surgical dissection and insufficient closure of afferent lymphatic vessels. Lymphocele is the most frequent complication after PLND. Lymphoceles are generally subclinical. Pelvic pressure, urinary frequency, deep venous thrombosis, ileus, infection and edema are the common symptoms.

In PCa cases, PLND is the most effective procedure for accurate cancer staging and removes all tumor deposits. Intraoperative complications related with PLND include ureteral, obturator nerve (sensory/motor neuropraxia) and major vascular injury.

Its incidence changes from 0% to 8% according to different reports. In a subgroup analysis, Davis *et al.*[53] found the rate of the symptomatic lymphoceles as 19% after extraperitoneal RARP, but 0% after transperitoneal RARP. The incidence of the PLND associated grade 3 and grade 4 complications during RARP vary from 0% to 5%. Only PLND related complications are rare. Any vascular injury necessitating transfusion or conversion to open surgery related with PLND were not reported yet[53]. Van der Poel *et al.*[54] observed no significant difference among the complication incidences between men undergoing PLND or not.

In a recent report, Briganti *et al.*[55] revealed that the rate of lymphocele was significantly increased (10.3%) in extended PLND as compared with limited PLND (4.6%). Accordingly, Naselli *et al.*[56] reported that the number of LNs retrieved was an independent and statistically significant predictor of the symptomatic lymphocele occurrence.

Keskin *et al.*[57] reported the lymphocele rate as 9% in 521 patients RARP series. The number of the symptomatic lymphoceles was 13. All lymphocele cases were detected by ultrasound at the routine follow-up at the end of the postoperative 1st month. Lymphocele was unilateral in 43 patients and bilateral in 3. At the end of the postoperative 6th month, ultrasonographic findings regressed in only 11 of 46 cases (24%).

Percutaneous external drainage was performed to 7 patients. As the history of the patients assessed, 5 of the 7 patients who presented an infected lymphocele were the cases with diabetes mellitus. A patient who was diagnosed before the routine first month follow-up was also diabetic, and presented new-onset bilateral leg edema, urinary incontinence and fever at the postoperative 3rd week. Bilateral lymphoceles and deep venous thrombosis were detected by ultrasonography and immediately treated with antibiotics, bilateral drainage, bed rest and high dose of low molecular weight heparin. The symptomatic lymphocele incidence was as low as 2.5% in this study. Infection was the most common sign. Hydrocele, leg edema, incontinence, deep venous thrombosis and superficial phlebitis were rarely observed[58].

Taniguchi *et al.*[59] presented a patient with delayed lymphocele infection after RARP and PLND in a recent case report. The patient who did not have known risk factors for lymphocele, applied with the complaint of fever and fatigue after 6 months from the operation. Pelvic ultrasonography and computed tomography (CT) showed an 80 mm cystic lesion leading to displacement of the urinary bladder. Blood markers of infection were increased. Fluid collection was drained and drainage tube was placed. Methicillin-susceptible

S. aureus were isolated and empiric antibiotic treatment was replaced by cefazolin 4 g/day. At the 7th day, the drainage tube was removed due to reduction in lymphocele size. Two months after, CT showed no recurrence[59].

Thromboembolism

Thromboembolism includes deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE). It is a serious complication with a low incidence as < 1%[60]. Generally, redisposing factors are venous stasis, vascular damage and hypercoagulability. Intermittent compressive devices (ICDs) or low-molecular-weight heparin (LMWH) should be used in prophylaxis. ICDs reduce only the DVT rate, however LMWH reduces both the DVT and PTE rates significantly[61].

Trochar site hernia

Trocar site hernia (TSH) is a serious uncommon complication and mostly requires surgical intervention. The overall incidence ranges from 0% to 5.2%[62]. TSH was reported at 5 mm or even smaller port sites[63]. TSH may also develop at the complete fascial closure sites, even though fascial closure prevents TSH[64]. TSH may also develop despite the use of bladeless and radially dilating trocars that are designed specially to decrease the fascial and muscular defect size[65]. In facts, nearly 4 of the reported cases were shown as related with the high prevalence of the procedure RARP[66-68].

Predisposing situations for post-operative TSH development should be evaluated according to underlying mechanisms. Technical and surgical factors include the size of the trocar site fascial defect, use of the cutting or non-bladed trocars, time period of the surgery, port locations (midline or paramedian), excessive manipulation at the port site leading to stretching of the fascia layers, specimen retrieval, angle of the trocar insertion and fascial closure at the end of the procedure. Patient factors include obesity, some postoperative factors such as cough or chronic constipation resulting in increased intraabdominal pressure, and factors affecting wound healing such as chemotherapy, diabetes mellitus, infection, malnutrition or smoking[69].

Tsu *et al.*[70] published a TSH case report in 2013. Patient has the bilateral open inguinal herniography history with recurrence at the left side requiring subsequent laparoscopic hernioplasty. RARP with bilateral pelvic lymphadenectomy was performed by the 6-port trans-peritoneal approach described by Pick *et al.*[71]. The 12-mm periumbilical port site used for the camera was enlarged at the level of specimen retrieval. This enlarged port site and the 12-mm assistant port site were closed with polydiaxanone at the fascial level. A 5-mm assistant port and three 8-mm robotic arm ports were closed at the skin level only. On the postoperative 4th day, patient had abdominal pain, distension and notable tender bulge near the 8-mm robotic arm port scar. Abdominal radiographs revealed ileus and CT showed that the bowel herniated through a fascial defect at the left 8-mm port site. Mini laparotomy was performed over the defect. In exploration, a loop of small bowel was found as trapped between the external and internal oblique muscles. The bowel loops were returned to the peritoneal cavity. Fascial layers of the laparotomy were closed separately with polydiaxanone. The patient represented an uneventful recovery[70].

In classical laparoscopy, the fascial port sites smaller than 10 mm may not be closed since the technical difficulties. However, the robotic arms generate a larger torque in the abdominal wall[66]. This information explains why TSH occurs after RARP. Seamon *et al.*[66] advised inserting surgical plugs into the 8 mm port site fascial defects when fascia is not closed. To avoid an excessively large fascial defect and enlarged preperitoneal space, Spaliviero *et al.*[67] recommended inserting the 8 mm port at a 60°-90° angle and closing the fascial layers in patients with risk factors for hernia development.

Lim *et al.*[69] reported a small bowel obstruction case due to an interparietal trocar site hernia after RARP. They recommended that 8 mm robotic trocar sites, associated with a large peritoneal defect, should be carefully closed at the end of surgery.

Chiong *et al*.[65] reported the incidence of TSH as 0.66%, all occurring at sites of 12 mm trocars, even though with the use of bladeless, blunt trocars. Furthermore, they suggested to insert the trocar at least 40°-60° to the abdominal wall to reduce the TSH occurrence risk[65,72].

Routine fascial closure is not recommended as the TSH incidence is rare in 8 mm robotic trocar sites. Instead, removal of ports under direct visualization is recommended at the end of the procedure to make sure that bowel segments are not unawarely pulled into the port sites during the port removal and to assess the degree of peritoneal defect[69].

Vesicourethral anastomotic strictures

Vesicourethral anastomotic strictures (VUAS) are fibrotic narrowing of the vesicourethral anastomosis. The incidence is less than 1.4% in RARC series[73,74]. The mostly seen comorbid conditions related with anastomotic stenosis are older age, cigarette smoking, hypertension, coronaryartery disease, obesity, prior bladder surgery, diabetes mellitus that affect vascular health, increase the tissue ischemia and result in poor healing. Anastomotic urine leakage, foreign body in urinary bladder, increased estimated blood loss and increased operative time that result in poor anastomotic mucosal apposition were also found as related with VUAS[75].

VUAS generally becomes symptomatic within 6 months following prostatectomy and the duration rarely prolongs up to 24 months[76]. Complaints related with voiding are primarily in obstructive pattern such as straining to void, weak stream, incomplete bladder emptying and hesitancy. Urinary retention and recurrent urinary tract infections may also indicate VUAS. Besides, the patients with radiotheraphy history often complain of urinary urgency and frequency, and dysuria.

Sandhu *et al*.[77] found VUAS rate as 4% (n = 198) in overall 4500 radical prostatectomy cases performed at Memorial Sloan-Kettering hospital. They detected the VUAS cases at an average of 3.5 months after prostatectomy. They were also found that the VUAS risk increased 10-folds in open procedures compared with minimal invasive methods[77].

In the management of VUAS, no consensus exists. Conservative management and open or minimally invasive surgical procedures may be a choice in the treatment plan. Patient preference is also important in decision. First-line management includes various endoscopic procedures, and complex reconstructive procedures may be applied in case of failure.

High-risk disease

D'Amico *et al*.[78] defined the high-risk disease as prostate-specific antigen level ≥ 20 ng/mL, preoperative Gleason grade ≥ 8 or clinical stage ≥ T2c by considering oncologic outcomes. Srougi *et al*.[79] performed RARP in 199 high-risk PCa cases and found their complication rate as 12.1% (4.5% as major complications). Jayram *et al*.[80] performed RARP in 148 PCa cases diagnosed as high-risk disease. They reported excellent complication rates as 0.6% in terms of minor complications (Clavien 1-2; urethral stricture) and 3.4% in terms of major complications (Clavien 3; lymphocele, hematoma/clot retantion and incisional hernia).

CONCLUSION

RARP can be routinely performed with a relatively low risk of complications. Surgical experience, cancer characteristics and clinical patient characteristics determine the risk of complications. Increased perioperative complications rates are significantly associated with low surgeon volume, low hospital volume and extended lymph node dissection. True patients selection, proper positioning, mentorship in the learning curve and avoiding prolonged procedures are important points in preventing RARP-related complications. Nevertheless RARP has low complication rates, it should be kept in mind that the complications may be devastating if not noticed. Thus surgeons should pay full attention in prevention and early management of complications.

DECLARATIONS

Authors' contributions

Manuscript preparation, literature search and data collection: Koc E
Study design and definition of intellectual content: Canda AE

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There are no conflicts of interest.

Patient consent

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Ethics approval

Not applicable.

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Mini-invasive Surgery

Case Report

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Successful treatment for infected biloma after endoscopic ultrasound-guided hepaticogastrostomy using double stent placement technique

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Abstract

This case report describes a treatment of an elderly man who had undergone pancreaticoduodenectomy (Whipple Procedure) due to bile duct cancer. Herein, we describe technical tips of endoscopic ultrasound (EUS)-guided hepaticojejunostomy EUS-HJS combined with EUS-guided antegrade stenting (EUS-AS) using novel plastic stent. First, intrahepatic bile duct was punctured using 19G fine needle aspiration needle. Next, the 0.025-inch guidewire was inserted into the biliary tract. After the guidewire was advanced into the intestine, the bile duct and the intestine wall were dilated using by balloon catheter. The covered metal stent delivery system was antegradely inserted across the stricture site, and stent placement was performed from the intestine to the bile duct. Finally, stent placement from the intrahepatic bile duct to the intestine using novel plastic stent was successfully performed without any adverse events.

Keywords: Endoscopic ultrasound, endoscopic ultrasound-guided hepaticojejunostomy, liver abscess, endoscopic ultrasound-guided biliary drainage

INTRODUCTION

Trans-jejunum biliary drainage with endoscopic ultrasound (EUS)-guided hepaticojejunostomy (EUS-HJS) is now a well established procedure[1]. However, EUS-guided biliary drainage (EUS-BD) procedures have possibility of several adverse events such as stent migration or bile leakage. To prevent these adverse events, a covered, self-expandable, metal stent (CSEMS) is usually selected and EUS-BD is sometimes combined with EUS-guided antegrade stenting (AS). If CSEMS obstruction occurs, re-intervention is challenging in

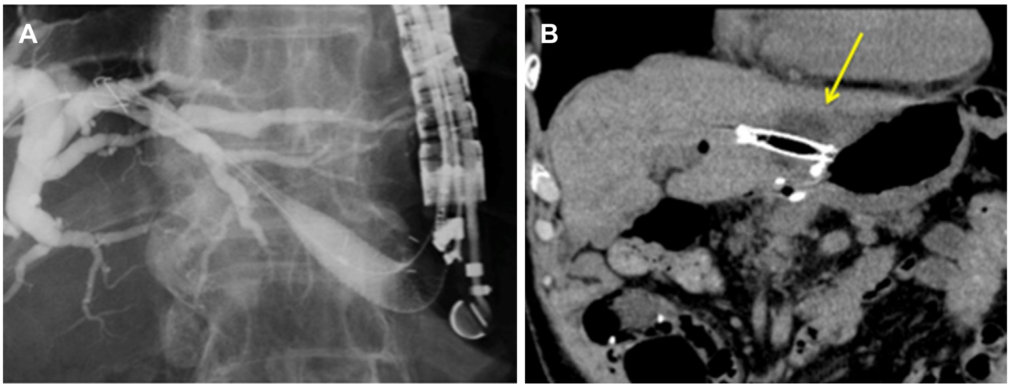

Figure 1. (A) Endoscopic ultrasound-guided hepaticogastrostomy using covered metal stent; (B) infected biloma is seen around endoscopic ultrasound-guided hepaticojejunostomy stent (arrow)

patients with a history of EUS-HJS because of limited lumen space compared with the stomach. Also, due to large diameter of EUS-HJS stent, bile juice reflux may cause vomiting. Recently, novel plastic stent has been introduced available in Japan. The plastic stent, which is a push-type stent and usually not possible to retract, has a total length of 20 cm, an effective length of 15 cm, and 4 flanges. The proximal end has a pigtail structure to prevent stent migration and the distal end is tapered[2,3]. This plastic stent has clinical impact because it is able to prevent stent migration into the abdominal cavity.

Although EUS-guided biliary drainage, such as hepaticogastrostomy (HGS), offers an alternative method to percutaneous transhepatic biliary drainage[2-5], various adverse events such as stent migration into the abdominal cavity are associated with EUS-HGS and considerable effort has been directed towards preventing them[4,5]. Despite these efforts, adverse events such as infected biloma after EUS-HGS still arise due to frequent reflux cholangitis through EUS-HGS stent, or bile duct obstruction by a covered metal stent[6]. A longer HGS stent may help to prevent reflux cholangitis[5], but if infected biloma occurs around an EUS-HGS, the stent must be exchanged. Other adverse events including liver abscess, may occur due to various reasons, and should be treated[7-11]. Here, we describe treatment of a liver abscess around an EUS-HGS, using double stent placement stent in an elderly man who had a history of surgery for bile duct cancer.

CASE REPORT

A 78-year-old man who had undergone pancreaticoduodenectomy due to bile duct cancer 1 year previously, was admitted to our hospital with obstructive jaundice. A benign bile-jejunum anastomosis stricture was diagnosed with computed tomography. Because the patient declined to undergo percutaneous drainage, the doctor proposed an alterative EUS-HGS procedure. The procedure was performed using a 10 mm × 10 cm, Niti-S Biliary Covered Stent (partially-covered, TaeWoong Medical, Seoul, South Korea; Century Medical Inc., Tokyo, Japan) [Figure 1A]. This resolved the obstructive jaundice, no adverse events occurred, and the patient was discharged after 2 weeks.

Four weeks after the EUS-HGS procedure, the patient presented with a fever and elevated inflammatory indicators and was consequently readmitted to hospital. Computed tomography revealed a biloma around the EUS-HGS stent [Figure 1B]. This biloma was considered to be complicated with infection. Endoscopic treatment for infected biloma was attempted as follows. An endoscopic retrograde cholangiopancreatography (ERCP) catheter (MTW Endoskopie, Düsseldorf, Germany) was initially inserted into the biliary tract through the EUS-HGS stent. A 0.025-inch guidewire (VisiGlide; Olympus Medical Systems, Tokyo, Japan) was inserted into the catheter and the metal stent was removed through

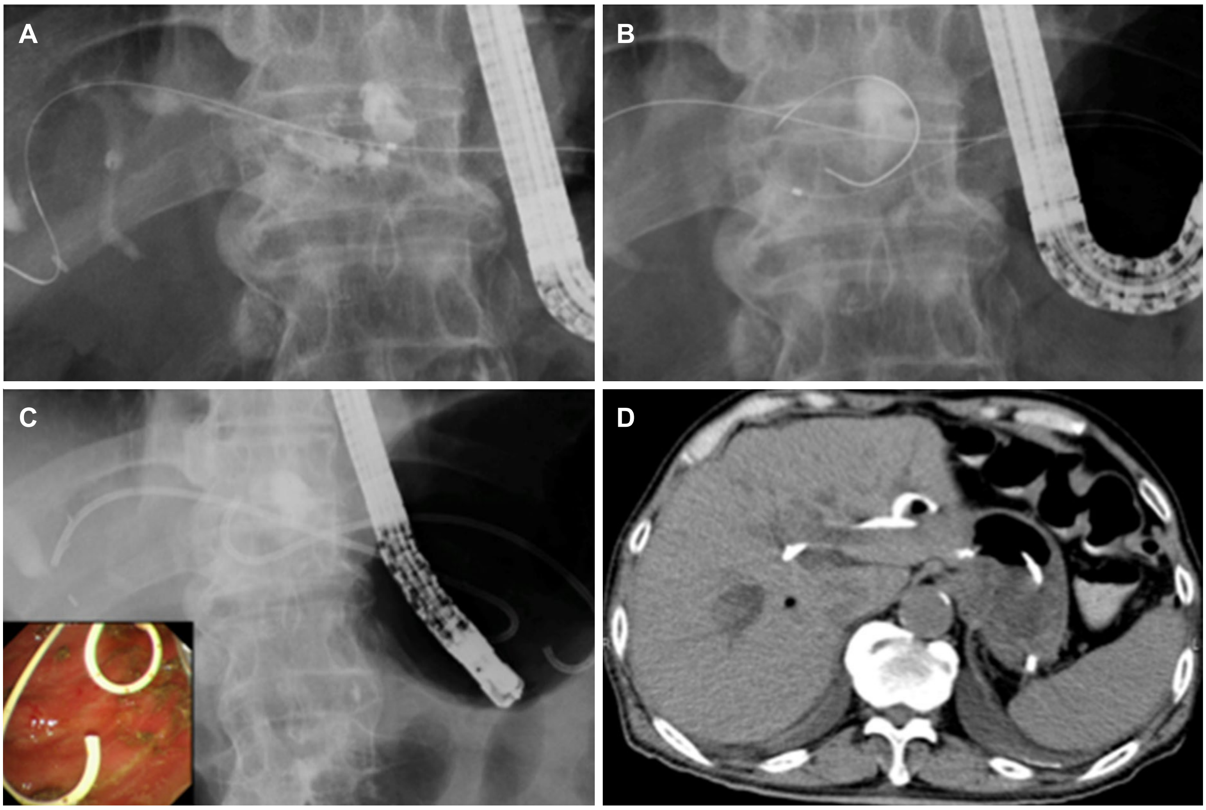

Figure 2. (A) Contrast-enhanced cholangioscopy image shows infected biloma; (B) guidewire placed in liver abscess and biliary tract; (C) deployed double stent; (D) computed tomography image after this procedure

the scope (JF 260V; Olympus Medical Systems, Tokyo, Japan). An additional ERCP catheter was inserted into the biliary tract, contrast medium was injected, and cholangiography visualized the infected biloma [Figure 2A]. Therefore, guidewires were inserted through the cateters in both the infected biloma and biliary tract [Figure 2B] so that a new EUS-HGS could be performed. A 7-Fr, double pig tail, 12-cm plastic stent (Medi-Globe GmbH; Achenmühle, Germany) was placed from the infected biloma to the stomach. Finally, a new, plastic stent placement (Type IT; Gadelius Medical Co, Ltd, Tokyo, Japan) was completed the EUS-HGS proedure [Figure 2C].

Thereafter, after 1 week, inflammatory indicators and clinical symptoms were immediately resolved and the patient was discharged. This stent was removed after 2 months, and recurrence of biloma was not seen.

DISCUSSION

Fully covered metal stents deployed via EUS-HGS offer several advantages. Bile leakage from the gap between a fully covered metal stent and a fistula created during EUS-HGS to insert various devices may be less likely. This type of stent also remains patent for longer periods than plastic stents[11]. In addition, a fully covered metal stent itself can confer a tamponed effect on bleeding from the stomach wall or vessels around the bile duct. The disadvantages of metal stents include high cost, potential for branch bile duct obstruction, and the possibility of shortening. Focal cholangitis due to branch bile duct obstruction by a covered metal stent deployed after EUS-HGS is an adverse event that can usually be conservatively treated[12]. However, a complicating, infected biloma is likely to require intervention. Kumata *et al.*[12] described a hepatic abscess that developed within the cavity between the stomach and liver after EUS-HGS. A 15-mm, lumen-apposing metal stent was deployed because the abscess could be accessed from the stomach and anchored by placing a plastic stent through it. The liver abscess in our patient was located in the hepatic parenchyma, which precluded the use of a lumen-apposing metal stent. Therefore, our technique is clinically useful for treating liver abscesses that arise after EUS-HGS, if percutaneous approach is refused by patients.

DECLARATIONS

Authors' contributions

Manuscript writing: Ogura T

Interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Ogura T, Okuda A, Miyano A, Nishioka N, Higuchi K

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

Not applicable.

Copyright

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Mini-invasive Surgery

Original Article

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Towards safe and efficient cervical dilatation

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Abstract

Aim: Traditional methods of cervical dilatation such as Hegar rods and laminaria are associated with the damage leading to the risk of cervical incompetence or require two sessions with higher risk of infections. In this study, a new dilator based on expanding triple balloons is assessed.

Methods: Cervical dilation with the triple balloon was evaluated in 15 women with various indications. After measuring the diameter of the cervix the triple balloon was inserted and inflated for 5-7 min and thereafter measured again.

Results: This time was sufficient to achieve the diameter of 4.5-9.5 mm which allowed performing all planned procedures without any need for further dilatation except for one case with cervical stenosis.

Conclusion: Further studies are needed, but the triple dilating balloon might become the optimal dilatation method for universal use.

Keywords: Cervical dilatation, hysteroscopy, abortion

INTRODUCTION

The Muellerian ducts are being formed from the paramesonephric cells and are creating the uterine body and the cervix. The endometrium has its unique, hormonally dependent cyclic pattern and the cervical mucous layer shows different cyclic characteristics[1]. Despite the common origin of the different elements of the uterus, their tissue architecture is different: smooth muscle in the lower third of the cervix is 6.4%, 18% in the middle third and 28.8% in the upper third, in the body of the uterus it is 68.8%[2]. The muscle tissue of the uterus is different from other striated muscles in the body. It is retractile, which means that it is able to rest while being contracted[3]. The cervix does not function as other sphincters in the body and expands passively and gradually as it is a fibrous organ which contains hyaluronic acid, collagen and proteoglycan[4].

Most intrauterine procedures need dilatation of the cervix in order to be able to introduce optical or surgical devices. As most of the cervix is composed of fibrous tissue and just small part of it is muscle, dilatation of the cervix without being originally primed by hormones as is the case during delivery, is certainly a non-physiological process. Therefore it is common that cervical dilatation by itself is associated with crucial pain if anesthesia is not used and involves the risk of the cervical incompetence in the future[5].

The cervical incompetence as the result of dilatation with Hegar rods and curettage is likely to be due to the damage occurring from the stretching of fibrous tissues of the cervix in two directions (longitudinal and transverse)[6].

Using laminaria causes only tranverse streching of the tissues and the dilatation occurs gradually over several hours. Gradual dilatation and softening of the dilating cervix reduce the risk of injuries and perforation[7]; anesthesia is not needed, however two sessions are mandatory for insertion and removal and dilation procedure takes several hours.

Both Hegar rods and laminaria have been in use for many years for dilatation. Recently, a new method was introduced. It is a 3-mm diameter triple balloon which is easily inserted into the uterus, anchored; and the two dilating balloons are inflated with saline creating lateral pressure of up to 6 bars which results in gradual dilatation of the cervix up to 8-9 mm within 5-7 min. The method is less painful and anesthesia usually is not needed unless surgical procedures are planned.

METHODS

Subject selection

The study included 15 women undergoing termination of pregnancy for different indications.

Inclusion criteria

1. Females with 18 years of age or older;
2. Subjects undergoing termination of pregnancy;
3. Subjects willing to sign informed consent form.

Exclusion criteria

1. Subjects younger than 18 years of age;
2. Subjects unwilling or unable to sign the informed consent form.

Description

The device is compound of three balloons and a catheter. The distal balloon anchors the device in its place beyond the internal Os. Two elongated dilating balloons are designed in order to enable efficient dilation of any cervices ranging in length from 3 to 7 cm. The outer diameter of the deflated semi-rigid catheter is 7 French (2.3 mm), enabling easy insertion of the catheter in the cervical canal. Prior to the dilation, the dimeter of the cervix is measured with calibrated Hegar rods.

The catheter with deflated balloons [Figure 1] is inserted through the cervix into the uterus. An anchoring balloon is inflated through the “anchor channel” [Figure 1] with 2.5 mL syringe with 1.5 mL of saline

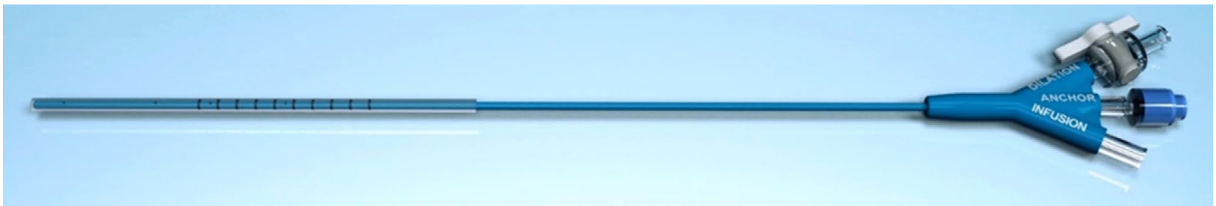

Figure 1. The triple balloon catheter - deflated balloons (cited from Weichselbaum and Stark[6] with permission)

Figure 2. The triple-balloon catheter - inflated balloons (frontal anchor balloons and two elongated dilating balloons) (cited from Weichselbaum and Stark[6] with permission)

solution. Both elongated dilating balloons are then inflated simultaneously at each end of the cervical canal (internal and external Os) by injections of 2.5 mL saline through the "dilation channel". The surgeon can control the inflation rate and dilate the cervix gradually according to the resistance created. The inflation of the dilating balloon takes around 10 s, and the inflated balloons stay in the cervical canal up to 7 min depending on the needed diameter [Figure 2]. In the next stage, saline solution is injected into the cervical canal between the two dilating balloons through the "infusion channel" for washing and lubricating of the cervix. For catheter removal, the balloons are deflated. For the final cervical diameter assessment, the cervix is measured again by calibrated Hegar rods.

The device was used in 15 women at the Yoseftal Hospital in Eilat, Israel in patients where dilatation of the cervix was indicated for various procedures. The study was approved by the Hospital Ethical Committee and all participants signed informed consent form. The aim of the study was to find out if the triple balloon catheter could be a valid alternative to the traditional dilatation with Hegar rods.

Procedure started with patients in lithotomy position, thorough cleaning of the vulva and the vagina. After the patient was covered, speculum was inserted, the upper part of the cervix was grasped with tenaculum forceps and the diameter of the cervix was measured with calibrated Hegar rods. The triple balloon catheter was thereafter inserted into the cervix without difficulties except one case where cervical stenosis did not enable its insertion. The anchor balloon was inflated and the catheter was gently pulled out until it was fixed in the optimal position and thereafter the two elongated dilating balloons were inflated and left *in situ* for 5-7 min. The cervix was lubricated with saline solution between both dilating balloons and then the catheter was removed and the diameter of the dilated cervix was measured again with calibrated Hegar rods.

RESULTS

The details of the clinical outcome are summarized in Table 1. The average age of the patients was 29.1 years. The minimal diameter of the cervix prior to the dilatation was 2 mm and the maximal was 4.5 mm. After the dilatation with the balloon catheter, the minimal diameter of the cervix was measured as 4.5 mm and the maximal was 9.5 mm. With the exception of one case which was clinically diagnosed as cervical stenosis, all the needed intrauterine procedures were done without any need for additional dilatation with other methods.

Table 1. Outcome of cervical dilatation with triple catheter in 15 cases

Case	Age, years	G (gravity), D (delivery)	Cervix diameter	
			Before dilatation	After dilatation
1	33	G1D0	4	9
2	25	G1D0	4	8
3	18	G1D0	4.5	8
4	20	G1D0	2.5	Cervix stenosis
5	19	G1D0	3	7
6	21	G1D0	3.5	8
7	24	G2D0	3	8
8	38	G4D3	3	5.5
9	42	G3D2	4	9
10	32	G1D0	2.5	9.5
11	42	G3D2	4	9
12	27	G1D0	3.5	9
13	37	G4D4	2	4.5
14	29	G6D5	2	5
15	30	G3D2	2.5	5.5

DISCUSSION

Cervical dilatation with Hegar rods is used all-over the world however with the risk of future cervical incompetence which is higher in nulliparous. During the dilation with Hegar rods, the cervix is stretched in two different directions, longitudinal and radial, which can be damaging because the cervix consists of mainly fibrous tissue and collagen although the percentage of collagen varies with cervical pathologies[8]. This is in contrast to the body of the uterus where the percentage of the muscular tissue is significantly higher than in the cervix[6]. The balloon catheter has the advantage over Hegar rods because it does not stretch the cervical walls longitudinally, and so minimizing or eliminating the risk of the damage to the cervical tissue.

Laminaria is associated with lower risk of damage to the cervical wall but the balloon catheter has advantage over it because desired dilatation can be achieved in several minutes versus hours and two sittings needed when laminaria is used.

Dilating balloons allowed to successfully dilate the cervix to the desired diameter in all cases except the diagnosed cervical stenosis and the dilatation was sufficient for all the planned procedures. No vasovagal attack incidence was recorded during the study.

A novel method to dilate the cervix whenever it is indicated is presented. The balloon catheter proved to be user-friendly, efficient and is not associated with risks of damage to the cervical wall and potential cervical incompetence.

This pilot study shows that the balloon catheter is a promising method but more studies will be needed in order to prove its efficiency and its potential for universal use for any indication of cervical dilatation.

DECLARATIONS

Authors' contributions

Manuscript preparation and data acquisition: Stark M
Literature search: Stark M
Surgery: Tzabari A
Data acquisition: Tzabari A
Study design and definition of intellectual content: Weichselbaum A

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Conflicts of interest
There are no conflicts of interest.

Patient consent
All participants signed informed consent form.

Ethics approval
The study was approved by the Hospital Ethical Committee.

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Mini-invasive Surgery

Original Article

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Does intra-operative cardiac output monitoring improve outcomes for patients undergoing elective colorectal surgery within an enhanced recovery programme?

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Abstract

Aim: Intra-operative cardiac output (CO) monitoring became a standard of care in Northampton General Hospital, UK, at the end of 2013. This study aimed to assess the effectiveness of intra-operative CO monitoring with oesophageal Doppler or LiDCO for patients undergoing elective colorectal surgery for cancer within an enhanced recovery after surgery (ERAS).

Methods: Data was prospectively collected over a 5-year period (March 2010 - Feb 2015) for patients undergoing elective colorectal surgery in the practice of a single surgeon. The ERAS protocol was applied for all the patients. There were 69 patients who had intra-operative CO monitoring with oesophageal Doppler or LiDCO and 144 patients who had no intra-operative CO monitoring. Results were analysed for post-operative outcomes (morbidity, mortality, readmission within 30 days, total length of hospital stay and admission to a high level of care facility).

Results: There was no significant difference in 30-day morbidity and readmission rates between the two examined groups. Forty-six percent of patients in the intra-operative CO monitoring group were admitted to a low level of care facility (ward) in comparison to 24% of patients in the no intra-operative CO monitoring group (P = 0.01).

Conclusion: Using intra-operative CO monitoring singnificantly might reduce the need for admission to critical care. A larger cohort study is needed to further confirm these findings and account for any co-founders.

Keywords: Non-invasive cardiac output monitoring, enhanced recovery, colorectal surgery, outcomes, perioperative care

INTRODUCTION

Intra-operative cardiac output (CO) monitoring facilitates goal-directed intra operative fluid therapy (GDFT), a constituent of enhanced recovery pathways, which using a series of pre-, intra-and post-operative guidelines[1], has been shown to improve patient recovery after major surgery. These programmes have been shown to reduce the length of hospital stay, readmissions, and 30-day morbidity[2-8].

Intra-operative fluid administration is important in preventing hypovolaemia and its complications including hypo-perfusion, impaired wound healing, anastomotic leak[9,10] and a systemic inflammatory response[2], but there has been much debate in the literature about which intra-operative fluid (IOF) regimen is best for patients undergoing both open and laparoscopic colorectal surgery, with many advocating restrictive, more liberal or goal-directed fluid regimens with the aim of improving patient outcomes.

Restrictive regimens have been shown to be advantageous, reducing post-operative complications[11-15], whereas liberal fluid administration has been associated with fluid overload and complications such as a reduction in gut motility, mucosal oedema and an increased risk of anastomotic breakdown[16,17]. It is also associated with pulmonary oedema and cardiac dysrhythmias[15,18-20]. GDFT aims to use dynamic measurements of cardiac output to guide IOF administration to maintain a "zero fluid balance" and thus reduce complications associated with inappropriate peri-operative fluid administration.

GDFT is achieved by monitoring cardiac output through various techniques, including the gold standard - pulmonary artery catheter-based thermodilution, but this is an invasive procedure associated with complications such as perforation of the pulmonary artery[21]. Vital sign measurements such as blood pressure and heart rate are not adequately specific or sensitive to guide fluid administration. Central venous pressure (CVP) monitoring has also been used, but this is limited in colorectal surgery where the patient is in the Trendelenburg position, creating a falsely elevated CVP by raising intrathoracic pressure, and has been shown to be an ineffective guide for IOF therapy[22]. Other techniques of continuous CO monitoring include oesophageal Doppler (CardioQ, Deltex Medical Ltd, Chichester, UK) and arterial pressure (AP) waveform analysis (LiDCO, LiDCO Ltd, Cambridge, UK) amongst others[23,24].

Although there are many studies assessing the value of restrictive or liberal fluid regimens, further investigation into the role of GDFT and CO monitoring in intraoperative fluid administration and its role on patient outcomes is needed.

The aim of this study was to compare the surgical outcome measures between 2 groups of patients (those who received intra-operative CO monitoring using the oesophageal Doppler or LiDCO and those who had no intraoperative CO monitoring) who underwent elective colorectal surgery in an enhanced recovery programme.

METHODS

Data was prospectively collected over a 5-year period (March 2010 - Feb 2015) for patients undergoing elective colorectal surgery in a single surgeon's practice. Data collection and analysis were performed by two observers. Surgical outcome measures included 30- and 90-day mortality, morbidity, readmission, length of hospital stay (LOS) and admission to a high level care facility [intensive care unit (ICU) or high dependency unit (HDU)]. With the introduction of intra-operative cardiac output monitoring with either oesophageal Doppler or LiDCO as a standard of care in patients on the ERAS pathways at the end of 2013, we compared outcomes to those where no intra-operative cardiac output monitoring was used prior to this time. All the patients were cared for on the enhanced recovery after surgery (ERAS) pathways. Statistical analysis and inter-group comparisons were made using the Mann-Whitney *U* test. A *P*-value of < 0.05 was deemed statistically significant.

Table 1. Patient characteristics for the intra-operative CO monitoring group (treatment group) and the no intra-operative CO monitoring group (control group)

Characteristics	Treatment group	Control group	*P*
Number	69	144	
Age (years), median (range)	68 (22-87)	70 (37-93)	NS
Gender, M:F	37:32	74:70	NS
Mode of surgery, *n* (%)			
Routine	59 (85.5)	124 (86.1)	NS
Emergency	10 (14.5)	20 (13.9)	
ASA, *n* (%)			
I	6 (8.6)	6 (4.2)	NS
II	38 (55)	91 (63.2)	
III	22 (32)	42 (29.1)	
IV	1 (1.5)	4 (2.8)	
Unknown	2 (2.9)	1 (0.7)	
Operation type, *n* (%)			
Right colonic surgery	19 (27.5)	52 (36)	NS
Left colonic/rectal surgery	50 (72.5)	92 (64)	
Cancer:benign	57:12 (82.6:17.4)	133:11 (92.4:7.6)	0.05
Lap:Open:Conv	48:14:7 (69.5:20.3:10.2)	82:35:27 (57:24:19)	0.05
Intra-operative systolic BP	132 (80-193)	138 (95-190)	NS
Intra-operative heart rate	77 (56-109)	74 (56-110)	
Operation time (min)	168 (48-365)	158 (45-380)	

NS: not significant ($P > 0.05$); M:F: male to female ratio; ASA: American Society of Anaesthesiologists; BP: blood pressure; Lap: laparoscopic; Conv: converted to open surgery

RESULTS

Two-hundred and thirty nine patients were reviewed (intra-operative CO monitoring, n = 69 and no intra-operative CO monitoring, n = 144). Post-operative outcomes were analysed. Most baseline characteristics were similar for both groups of patients [Table 1]. There was a statistically significant higher number of patients undergoing open surgery in the group with no intra-operative cardiac output monitoring (P = 0.05). There was also a statistically significant increase in the number of patients who had surgery for cancer in this group (P = 0.05). The greater number of patients in this group may explain this finding.

Only one patient died in this cohort within 30 days (in the no intra-operative CO monitoring group). There was no significant difference in the 30-day Clavien-Dindo morbidity (III-IV) for the two groups (5.7 *vs.* 5.5, P = 0.13). The median length of post-operative hospital stay for the treatment group was 6 days in comparison with 7 days for the control group. The difference in length of post-operative hospital stay between both groups was not statistically significant (P = 0.059). There was no statistically significant difference in 30-day readmission rate for both groups (10.1% *vs.* 5.5%) (P = 0.064).

A significantly higher proportion of patients (46.5%) were admitted to level 2/3 care facility for patients in the treatment group in comparison with patients in the control group (24%, P = 0.01) [Table 2]. Twenty-four percent of patients were admitted to high dependency unit (level 2 care) in the treatment group whereas 39% of patients were admitted to level 2 care facility in control group. The median length of stay (2 days) in the high dependency unit (level 2 care) remained the same for both groups. No patients in the treatment group were admitted to the ICU. However, 11 patients (7.6%) were admitted to ICU in the control group.

DISCUSSION

The study found that patients with intra-operative cardiac output monitoring and goal directed fluid therapy had a reduced number of admissions to levels 2 and 3 care compared with patients receiving no intra-operative CO monitoring or GDFT. HDU admissions were 24% in the treatment group and 39% in the control group. No patients were admitted to ICU in the treatment group whereas 7.6% of patients were

Table 2. Comparisons of the post-operative outcomes for the intra-operative CO monitoring group (treatment group) and the no intra-operative CO monitoring group (control group)

Post-operative outcomes	Treatment group	Control group	*P*
30-day mortality	0	1	NS
90-day mortality	0	0	
30-day morbidity	0	0	
Clavien-Dindo III-IV, *n* (%)	4 (5.7)	8 (5.5)	
Readmission in 30days, *n* (%)	7 (10.1)	8 (5.5)	
Length of hospital stay (days), median (range)	6 (2-92)	7 (2 -112)	
Length of stay in HDU			0.01
Patients, *n* (%)	17 (24)	56 (39)	
Median (range) days	2 (1-6)	2 (1-13)	
Length of stay in ICU			
Patients, *n* (%)	0	11 (7.6)	
Median (range) days		2 (1-15)	

NS: not significant ($P > 0.05$); HDU: high dependency unit (level 2 - patients needing single organ support excluding mechanical ventilation such as renal hemofiltration or inotropes and invasive blood pressure monitoring. Staffed with one nurse to two patients); ICU: intensive care unit (level 3 - patient requiring two or more organ support or needing mechanical ventilation alone. Staffed with one nurse for per patient and usually with a doctor present in unit 24 h per day)

admitted to ICU in the control group. This could be due to several reasons: firstly, it may be that patients with intraoperative CO monitoring received optimised fluid therapy and subsequently required lower level of care, but the lack of data for the volumes of fluid administered to all patients leaves us unable to draw this conclusion. Secondly, CO monitoring provided the anaesthetists with up-to-date and accurate data about cardiovascular status and stability and may have influenced the need for postoperative care, hence, patients who were performing well having their care needs downgraded. Thirdly, adequate fluid administration intraoperatively would have reduced GI complications resulting from fluid overload or hypovolaemia. Fluid overload can lead to several harmful effects such as, generalised oedema, hindering tissue healing, detrimental effects on cardio-pulmonary functions, delayed recovery of gut functions[9], decreased muscular oxygen tension[10], increased risk of complications[11,12] and is linked to poor survival rates[13]. The effectiveness of intra-operative cardiovascular monitoring to reduce such complications has been proven in other published studies[25-30]. On the other hand, hypovolemia can lead to hypoperfusion, circulatory collapse, impaired wound healing, anastomotic leak[14,15], bacterial translocations and endo-toxaemia with activation of the systemic inflammatory response[31]; all of which account for the need of prolonged stay in high level care facilities post-operatively. Noblett *et al.*[2] have shown a reduction in peak systemic inflammatory cytokine (IL-6) levels for patients undergoing CO monitoring with Doppler. This study concluded that the Doppler intervention reduced the systemic inflammatory response to surgical trauma, preserved splanchnic perfusion and thereby reduced gut-related inflammatory responses. Fourthly, results could also have been affected by the fact that, within the control group, more patients had open surgical procedures for malignancy, and many cases were converted to open (n = 27), thus those patients, subsequently, required more HDU/ICU admissions. Therefore, the availability of intra-operative CO data in that patient group would have influenced the decision for admission to HDU/ICU care is not known.

The median length of hospital stay for treatment group was shorter in comparison to control group (6 *vs.* 7 days). But, this difference did not reach statistical significance ($P = 0.078$). All patients in the treatment and control groups were cared for on the ERAS programme. Outcomes associated with ERAS are dependent on multiple peri-operative factors.

The limitations of this study are a lack of data about the accurate volume of intra-operative fluids administrated, intra-operative CO variations, P-POSSUM scores and the rationale of the decision for admission to different levels of post-operative care areas. Availability of such data would have allowed adjusting for these confounding factors to assess post-operative outcomes more accurately. This study lacks the data about study population representative for other surgeons, variability in ethnicity and socioeconomic status. More patients in the control period had open operations and more had conversions from laparoscopic to open procedures that during the CO measurement period. Patients in the earlier period may have required more advanced care because of the higher level of invasiveness of the operation. These differences alone would explain a large percentage of the change in level 2/3 care required in the earlier period, and not the implementation of CO monitoring. Due to the lack of data about the precise decision for admission in ICU/HDU in the control group did not allow analysis for these co-founders. The authors did not notice a change in practice for the use of bowel preparation for colon surgery patients. No mechanical bowel preparation is used at the unit for right colonic surgery and only Phosphate enema is used for left sided colonic and rectal surgery. Enhanced recovery protocols have recommended the elimination of mechanical bowel preparation which would reduce IV volume support for patients undergoing colorectal surgery. Though practice for bowel preparation did not change in study period, a lack of data in the consistency in bowel preparation over the entire time of the study highlights the issue that even a minor change in practice combined with less invasive surgical procedures makes the postoperative care of the patients in the two periods of time very different.

Intra-operative indices of tissue hypo-perfusion resulting in gastrointestinal dysfunction are the most common post-operative complications in patients undergoing moderate-to high risk emergency GI surgery. Intra-operative CO optimisation and GDFT for patients undergoing colorectal surgery reduces the post-operative morbidity, mortality and length of hospital stay[9]. GDFT has also been shown to be cost effective in reducing hospital stays and the surgical complications[32,33]. It would be interesting to extend this study to use intra-operative cardiac output monitoring for patients undergoing emergency laparotomy and to assess the outcomes through the National Emergency Laparotomy Audit.

In conclusion, the use of intra-operative cardiac monitoring does not significantly alter the immediate post-operative outcomes; however, it reduces the need for admission to level 2/3 care facilities post-operatively. Intra-operative cardiac output monitoring might become an effective way to reduce the need for higher level critical care beds in patients undergoing elective colorectal surgery. A larger cohort study is needed to further confirm these findings and account for any co-founders.

DECLARATIONS

Authors' contributions

Conception and design: Merchant J, Evans R, Ihedioha U, Kang P
Acquisition of data: Aslam MI, Smith H, Akhtar N
Analysis and interpretation of data: Aslam MI
Article drafting: Aslam MI, Smith H, Akhtar N
Revision for important intellectual content: Currow C, Merchant J, Evans R, Ihedioha U, Kang P
Final approval: Aslam MI, Smith H, Currow C, Akhtar N, Merchant J, Evans R, Ihedioha U, Kang P

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Conflicts of interest

There are no conflicts of interest.

Patient consent

No personal information for patients involved in the article.

Ethics approval

Ethics review was not required by the institution for a retrospective analysis for prospectively maintained database.

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Mini-invasive Surgery

Original Article

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A skill degradation in laparoscopic surgery after a long absence: assessment based on nephrectomy case

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Abstract

Aim: To examine the laparoscopic skill-degradation effect by investigating whether a long absence from laparoscopic surgery increases laparoscopic surgery time.

Methods: Using the Japanese Diagnosis Procedure Combination database from April 2010 to March 2012, data for patients undergoing laparoscopic nephrectomy and nephroureterectomy for malignancy were collected. To regulate the hospital volume effect, the hospitals included in the study were limited to those with hospital volumes of 12-24 per year. Laparoscopic time was assessed by multivariate linear regression analysis including interval days, age, gender, comorbidity, oncological stage, nephrectomy or nephroureterectomy, hospital academic status, and hospital volume.

Results: For intervals of ≥ 7 days (3057 cases), 8-14 days (1325 cases), 15-28 days (1424 cases), 29-56 days (711 cases), and ≤ 57 days (332 cases), the median laparoscopic times were 245, 247, 255, 265, and 260 min, respectively (P < 0.001). In multivariate analyses for laparoscopic time compared with interval of ≥ 7 days, 15-28 days, 29-56 days and ≤ 57 days were associated with slightly longer laparoscopic time (+10.5, +16.8, and +18.8 min, all P < 0.01, respectively).

Conclusion: Absence intervals of ≤ 15 days can slightly lengthen the operation time, which suggest the existence of mild degree of a skill-degradation effect in laparoscopic surgery.

Keywords: Clinical competence, laparoscopic nephrectomy, laparoscopic nephroureterectomy, learning curve, skill retention

INTRODUCTION

To improve and maintain surgical skill, practice repetition is necessary. Several papers have documented the existence of a learning curve and hospital volume effect in laparoscopic surgery. The learning curve represents the theory that performance level improves reliably practice by practice, while the hospital volume effect reflects the theory that operative outcomes are inversely related to procedure volume[1,2].

While both theories support the notion that frequent and repeated exposure to clinical surgery improves skill, the idea of a forgetting curve, a counterpart to these theories, is rarely mentioned. When opportunity for practice is limited, degradation of skill would progress in an inverse manner to the learning curve. Thus, we questioned whether laparoscopic skill decays after a long absence from laparoscopic surgery.

In a real clinical setting, surgery does not occur regularly. For example, at a hospital with experiences of 12 laparoscopic surgeries per year, the surgery occurs about once a month on average. However, two cases could appear within 1 week, while other cases could appear after an interval of 2 or 3 months. If skill-degradation occurs within a-few-months intervals, long intervals will link to poorer outcomes, than short intervals. To the best of our knowledge, the effect of a long absence on laparoscopic surgical skill has not been evaluated.

In the present study, we tested the hypothesis that laparoscopic surgery time would become longer and longer according to increasing duration of absence, by analyzing a large number of laparoscopic nephrectomy and nephroureterectomy cases from multiple centers.

METHODS

Case selection and endpoint

The patient data used in the present study were selected from a Japanese nationwide clinical administrative database named the Diagnosis Procedure Combination database during the fiscal years of 2010 to 2012. The database holds clinical information collected from about 1000 hospitals throughout Japan, and covers approximately 50% of all acute-care hospitalizations[3,4].

The selected patients underwent laparoscopic nephrectomy and nephroureterectomy (Japanese surgical code, K773-2) for malignancy of the kidney, pelvis, and ureter (International Classification of Diseases and Related Health Problems 10th Revision codes, C64, C65, and C66, respectively). To calculate interval of laparoscopic experience accurately, other laparoscopic surgeries which urologists potentially performed including laparoscopic adrenalectomy, pyeloplasty and prostatectomy (K754-2, K755-2, K756-2, K778-2 and K843-2) were also extracted from the database. The interval to surgery was calculated based on the date of laparoscopic nephrectomy, nephroureterectomy, adrenalectomy, pyeloplasty and prostatectomy. As surgery time itself was not included in the database, the endpoint of the study was set as the laparoscopic time which was measured by the period of pneumoperitoneum with Japanese surgical code of L008-4.

The inclusion criteria for the hospitals were annual hospital volumes for laparoscopic nephrectomy and nephroureterectomy of 12-24 cases per year for the following two reasons. First, the interval to surgery was classified into five categories: ≤ 7 days, 8-14 days, 15-28 days, 29-56 days, and ≥ 57 days. Therefore, ideal hospitals for the investigation were those in which laparoscopic nephrectomy and nephroureterectomy were performed once or twice per month on average. Second, the range of hospital volume needed to be limited to regulate the hospital volume effect, a well-known factor affecting laparoscopic skill quality. If no restrictions were placed on hospital volume in the study, the group for interval of ≤ 7 days would be mainly occupied by cases from high-volume hospitals (e.g., ≥ 50 cases per year) and the group for interval of ≥ 57 days would be filled by cases from low-volume facilities (e.g., ≤ 5 cases per year). Such a large inconsistency in hospital volume among the interval categories would lead to a wide difference in laparoscopic skills at baseline.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was approved by the Institutional Review Board and Ethics Committee of The University of Tokyo (No. 3501).

Informed consent

Because the clinical data in the database were thoroughly de-identified and the study design was a secondary analysis of administrative claims data, informed consent from individual patients was not required.

Statistical analysis

First, the interval period was defined as the duration between the current case and the last laparoscopic case in the hospital. For example, when a laparoscopic nephrectomy was performed on April 30 and the previous procedure was carried out on April 20, the interval was 10 days. Tables showing the patient background data and distribution of laparoscopic time were constructed.

Second, the relationship between interval days and laparoscopic time was illustrated by adopting a method for restricted cubic spline curves, as a technique that allows flexible descriptions of non-linear relationships among variables[5,6].

Finally, multivariable linear regression analyses for laparoscopic time were performed with interval days and other adjusting variables including age, gender, comorbidity (in the form of the Charlson comorbidity index[7]), oncological stage (according to the International Union Against Cancer[8]), type of surgery (nephrectomy or nephroureterectomy), hospital academic status, and hospital volume. The hospital clustering effect was adjusted by a general equation estimation method[9]. In the multivariable analyses, missing values for oncological stage were regulated to avoid bias caused by incomplete data. This was achieved by performing multiple imputations to replace the missing values with a set of substituted plausible values by creating five filled-in copies using a method for polytomous regressions[10].

All statistical analyses were conducted using SPSS version 23.0 (IBM SPSS, Armonk, NY) and R version 3.0.2 software (R Foundation for Statistical Computing, Vienna, Austria) with the RMS 4.0-0 package[11,12]. Univariable comparisons were analyzed by the χ^2 test and Kruskal-Wallis test as appropriate. The threshold for significance was $P < 0.05$.

RESULTS

Overall, 6849 laparoscopic nephrectomy/nephroureterectomy cases were included from 222 hospitals. From the 222 hospitals, 750 laparoscopic adrenalectomy, 151 laparoscopic pyeloplasty and 816 laparoscopic prostatectomy cases were also identified. Intervals to laparoscopic surgery was calculated based on the total of 8566 cases, and the baseline characteristics in the interval groups are shown in Table 1. The long interval groups (≥ 29 days) were slightly biased toward advanced oncological stage, frequent nephrectomy, low hospital volume, low rate of academic hospitals, and longer laparoscopic time.

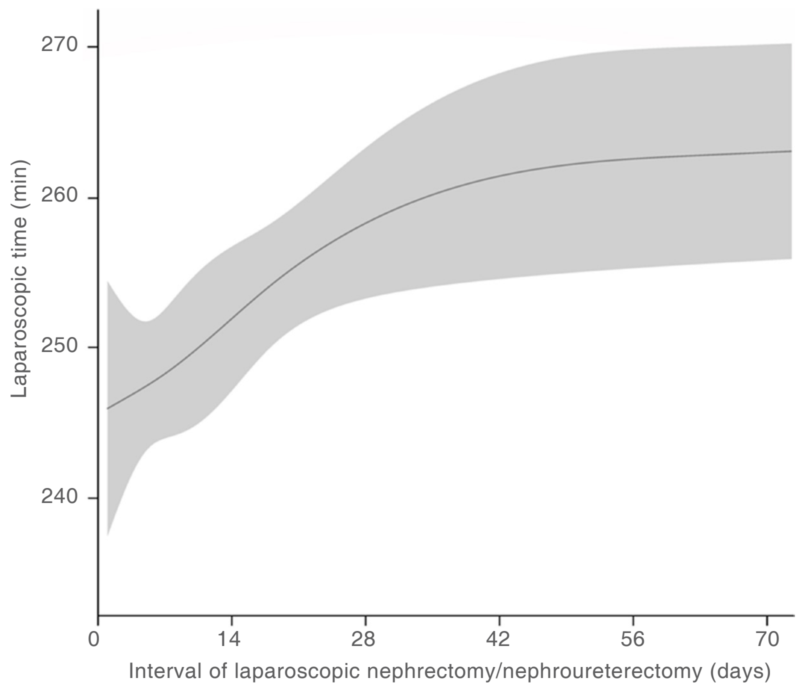

Figure 1. Relationship between laparoscopic time and interval days of laparoscopic nephrectomy/nephroureterectomy depicted by the restricted cubic spline curve method. The grey zone is the 95% confidence interval. Laparoscopic time increased significantly according to the interval days (P = 0.003; nonlinearity P = 0.021)

Table 1. Baseline characteristics among 6849 nephrectomy/nephroureterectomy cases Regarding selected hospitals, annual surgical hospital volumes ranged 12 to 24 cases per year

Characteristics	Interval days of laparoscopic nephrectomy/nephroureterectomy, *n* (%) or median (IQR)					*P*
	0-7	8-14	15-28	29-56	≥ 57	
	n = 3057	*n* = 1325	*n* = 1424	*n* = 711	*n* = 332	
Age	67 (59-75)	68 (60-76)	68 (60-75)	68 (60-75)	68 (59-76)	0.126
Male	991 (32.4)	432 (32.6)	436 (30.6)	215 (30.2)	107 (32.2)	0.615
Female	2066 (67.6)	893 (67.4)	988 (69.4)	496 (69.8)	225 (67.8)	
Charlson comorbidity index						
0	1827 (59.8)	746 (56.3)	840 (59.0)	389 (54.7)	185 (55.7)	0.187
1-2	886 (29.0)	417 (31.5)	407 (28.6)	229 (32.2)	102 (30.7)	
≥ 3	344 (11.3)	162 (12.2)	177 (12.4)	93 (13.1)	45 (13.6)	
Stage						
I/II	1653 (54.1)	770 (58.1)	840 (59.0)	445 (62.6)	207 (62.0)	< 0.001
III/IV	290 (9.5)	145 (10.9)	165 (11.6)	90 (12.7)	38 (11.4)	
Missing	1114 (36.4)	410 (30.9)	419 (29.4)	176 (24.8)	88 (26.5)	
Nephrectomy	1032 (33.8)	463 (34.9)	513 (36.0)	281 (39.5)	121 (36.4)	0.054
Nephroureterectomy	2025 (66.2)	862 (65.1)	911 (64.0)	430 (60.5)	211 (63.6)	
Hospital volume	18 (15-21)	18 (15-21)	17 (15-20)	16 (14-19)	16 (13-19)	< 0.001
Academic hospital						
Yes	1147 (41.6)	598 (41.6)	520 (36.0)	282 (34.9)	136 (33.6)	< 0.001
No	1607 (58.4)	841 (58.4)	923 (64.0)	526 (65.1)	269 (66.4)	
Laparoscopic time (min)						
Overall	245 (180-308)	247 (186-309)	255 (194-320)	265 (200-328)	260 (205-325)	< 0.001
Nephrectomy	245 (180-304)	246 (185-305)	255 (197-317)	265 (200-319)	262 (208-322)	< 0.001
Nephroureterectomy	245 (180-317)	250 (188-316)	255 (189-328)	268 (200-348)	260 (200-340)	0.002

Figure 1 shows the relationship between laparoscopic time and interval days of laparoscopic nephrectomy and nephroureterectomy. The grey zone is the 95% confidence interval. The univariate regression analysis using the restricted cubic spline curve revealed a significant increase in laparoscopic time for longer interval days (P = 0.001).

Table 2. Multivariate linear regression analysis for laparoscopic time among 6849 nephrectomy/nephroureterectomy cases in terms of preoperative interval days

	Difference (95% CI), min	*P*
Interval days (*vs.* 0-7 days as reference)		
8-14 days	2.7 (-4.8 to 10.2)	0.479
15-28 days	10.5 (2.9 to 18.1)	0.006
29-56 days	16.8 (7.4 to 26.2)	< 0.001
≥ 57 days	18.8 (6.2 to 31.3)	< 0.001
Age (continuous)	0.3 (-0.0 to 0.5)	0.019
Female (*vs.* male)	-18.9 (-25.0 to -12.9)	< 0.001
Charlson comorbidity index (continuous)	2.3 (0.9 to 3.8)	0.002
Stage III/IV (*vs.* I/II)	20.5 (11.1to 29.9)	< 0.001
Nephroureterectomy (*vs.* nephrectomy)	7.7 (1.4 to 13.9)	0.016
Hospital volume (continuous)	-0.7 (-1.5 to 0.0)	0.054
Academic hospital (*vs.* non)	5.7 (-0.1 to 11.6)	0.055

Table 2 displays the results of the multivariate analyses for laparoscopic time. After background adjustment, and compared with interval of ≤ 7 days, intervals of 15-28 days (+10.5 min, $P = 0.006$), 29-56 days (+16.8 min, $P < 0.001$) and ≥ 57 days (+18.8 min, $P < 0.001$) were associated with slightly longer laparoscopic time.

DISCUSSION

This study is the first to examine the skill-degradation effect for laparoscopic surgery by investigating the relationship between laparoscopic time and interval days of laparoscopic surgery on a real clinical basis, using nephrectomy and nephroureterectomy cases as an example. No differences in laparoscopic time were observed for intervals within 14 days, while slightly elongated time was detected for intervals longer than 15 days. Despite the interesting significant difference, an extension of 10.5-18.8 min (about 3%) in surgical time would be clinically acceptable. Thus, we can say that a skill-degradation effect after a long absence is present, but the effect size is limited and clinically acceptable.

A forgetting curve is an illustration that depicts how skill decays over time when it is not reinforced[13,14]. While a learning curve is widely acknowledged as a process of skill enhancement, the process of skill degradation known as the forgetting curve is rarely discussed in relation to clinical skill. A randomized study on novice medical students learning anesthesia described that the time required to complete tracheal intubation in a manikin using a laryngoscope worsened after 1 month in terms of complex laryngoscope devices, while traditional Macintosh laryngoscope users showed no decay in intubation time even after 1 month without further practice[15]. These findings suggested that freshly learned skills could dwindle after 1 month. As the study participants were medical students with no previous intubation experience, we consider that skill and knowledge maintenance in professionals are not discussed to the same extent as those in novices and trainers.

In the present study, the detected degradation level was mild. According to the multi-store model, memory is classified into short-term memory and long-term memory[16]. New knowledge and newly learned skills are first stored in the brain as short-term memory. With repetition of training and education and after competency of procedure and knowledge has been achieved, the memory shifts to long-term memory, which is less likely to be forgotten. The limited temporal changes observed in the present study suggest that the laparoscopic technique used as a professional skill was generally maintained at a competent level and substantially retained even after an absence of around 1 month. As other reasons, despite the long absence of a particular surgeon, the staff in an operating room usually experience frequent exposure to laparoscopic surgery performed by other surgeons in different clinical departments. The collaboration of these well-experienced staff would be helpful to compensate for a long gap in experience of an individual surgeon. Schneider *et al.*[17] suggested that a collaborative approach among surgeons would reduce the learning curve and improve outcomes in laparoscopic nephrectomy. Furthermore, several documents and videos useful for brushing up surgical skills are now easily available via the Internet, and these favorable multimedia educational tools can be useful to prevent a surgeon's skill from decaying[18].

Several limitations to the present study should be mentioned. First, we should the stress the lack of individual surgeon data or actual operation-room time because of the nature of the database. The interval for a particular surgeon's laparoscopic experience must be longer than that for a hospital. Therefore, our results were statistically robust in terms of operation intervals, and indicated that the skills of individual surgeons would be more well maintained even after a long absence. Second, the laparoscopic time we used in the present study could be affected by several clinical factors that were lacking in the database. For example, performance of lymph node dissection, transperitoneal or retroperitoneal approach, and method for bladder cuff resection (laparoscopic or open) have an impact on overall laparoscopic time. In addition, information regarding conversion to open surgery was not available. An amount of blood loss or Clavien-Dindo classification were not registered in the database, however, we believe that several types of technical difficulties would be directly reflected in elongating laparoscopic time. Third, another laparoscopic experience other than the five surgical modalities we extracted could be performed by surgeons. Based on the authors' clinical experience in Japan, we believe urologists would rarely perform other laparoscopic surgeries, however the concern could not be completely removed.

In conclusion, regarding laparoscopic nephrectomy and nephroureterectomy, an absence interval of more than 15 days lengthened the surgery time, although the difference was slight. The present results suggest the existence of a mild degree of a laparoscopic skill- degradation retention effect in laparoscopic surgery.

DECLARATIONS

Authors' contributions

Conception and design: Sugihara T
Acquisition of data: Yasunaga H, Matsui H, Fushimi K, Homma Y
Analysis and interpretation of data: Sugihara T
Drafting of the manuscript: Sugihara T
Critical revision of the manuscript for important intellectual content: Ishikawa A, Fujimura T, Fukuhara H, Homma Y, Kume H
Statistical analysis: Sugihara T
Obtaining funding: Yasunaga H, Matsui H, Fushimi K, Homma Y
Administrative, technical or material support: Yasunaga H, Matsui H, Homma Y, Kume H
Supervision: Yasunaga H, Ishikawa A, Fujimura T, Fukuhara H, Kume H

Data source and availability

The patient data used in the present study were selected from a Japanese nationwide clinical administrative database named the Diagnosis Procedure Combination database. Please have a contact to Prof. Yasunaga <yasunagah-tky@umin.ac.jp> for data request.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Patient consent

Not applicable.

Ethics approval
The present study was approved by the Institutional Review Board and Ethics Committee of The University of Tokyo (No. 3501).

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Mini-invasive Surgery

Review

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Robotic and laparoscopic urologic surgery ischemic preconditioning

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Abstract
Laparoscopic and robotic assisted surgeries have evolved from a limited surgical procedure to a major surgical technique during the last three decades. The indications increased incrementally. Despite its several advantages, it has some surgery and pneumoperitoneum related adverse effects and hemodynamic complications. One of them is the ischemia reperfusion injury (IRI) of the abdominal organs that can be developed secondary to pneumoperitoneum. IRI is also a risk factor for acute kidney injury in partial nephrectomy surgeries even performed via open, or laparoscopic/robotic assisted. To reduce or avoid the IRI related complications during laparoscopy and robotics, several alternative approaches were suggested including ischemic preconditioning (IPC). IPC is a phenomenon that promotes tissue tolerance to ischemia. Since it was first introduced, several studies evaluating its protective effects or mechanism of action have been published. Majority of them demonstrated its potent beneficial effects against IRI. Despite these favorable results, IPC has not yet been used in clinical settings routinely. The unknown parts of the exact mechanisms, the lack of standard protocols for its use such as the duration of clamping, the number of clamping cycles, using an early window or a late window, using local IP or remote IP, and the all remaining uncertainly about these aspects of the process might lead clinicians to be hesitant about its clinical use. In this study we discussed what we have in our hands regarding the effects of IRI and protective mechanisms of IPC, animal studies and clinical evidence of IPC, remote and local IPC, laparoscopy/robotics induced IRI, and role of laparoscopic/robotic IPC.

Keywords: Robotics, laparoscopy, urology, ischemic preconditioning

INTRODUCTION
Laparoscopic and subsequently developed robotic assisted surgeries have evolved from a limited surgical procedure to a major surgical technique during the last three decades. The indications were increased

incrementally. Today we can easily say that laparoscopic and robotic surgeries are the most common surgical procedures[1]. Despite its several advantages, it has some surgery and pneumoperitoneum related adverse effects and hemodynamic complications.

Ischemia-reperfusion injury (IRI) is a pathological condition characterized by initial undersupply of blood to an area or organ, and subsequent restoration of perfusion and concomitant reoxygenation. Interestingly, this ischemia and reperfusion produce a robust inflammation and oxidative response, and lead to the injury ("reperfusion injury") of microvascular endothelium and renal tubular epithelium[2,3]. IRI is a major cause of acute organ dysfunction[4]. CO_2 pneumoperitoneum is mandatory for visualization during laparoscopic and robotic surgeries. For that reason, it is very logical to infer that creating CO_2 pneumoperitoneum may lead tissue/organ ischemia during insufflation and reperfusion during desufflation, a kind of laparoscopy related IRI[5]. Schäfer and Krähenbühl[6] demonstrated that pneumoperitoneum leads to a 10%-80% reduction in the rate of blood flow to the intraabdominal organs, but they also reported the return of this reduction to the normal range after desufflation[6]. IRI is a risk factor for splanchnic organ injury and liver and kidney are among the intraabdominal organs most severely affected[7]. To reduce or avoid the complications related to laparoscopy and robotics, several alternative approaches such as gasless laparoscopy, lower pressure laparoscopy and ischemic preconditioning (IPC) are introduced. IRI is also a risk factor for acute kidney injury in partial nephrectomy surgeries even performed via open, or laparoscopic/robotic assisted. We know that partial nephrectomy is the treatment of choice for small, localized renal tumors[8], and it is generally performed with occlusion of kidney vascular supply, leading to IRI. To reduce this kind of injury, several methods are proposed and investigated in the literature such as early hilar unclamping[9], renal hypothermia[10], segmental renal artery clamping[11], and selective branch microdissection[12] (beyond the scope of this review), and IPC[13].

IPC is a phenomenon. It was first introduced in 1986 by Murry *et al.*[1]. In their study on dogs, they were able to show reduced myocardial infarct size by IPC[1]. Since then, in contrast to some small studies with conflicting results, several studies demonstrating its protective effects on kidney have been published.

This article will provide an updated summary of the effects of IRI and protective mechanisms of IPC. We will also discuss the animal studies and clinical evidence of IPC, remote and local IPC, laparoscopy/robotics induced IRI. The last section will review the main topic, role of laparoscopic/robotic IPC. For this purpose, an extensive search of literature in PubMed was performed. "Ischemia reperfusion injury" and "ischemic preconditioning" key words were used. It was not restricted to any year but language was restricted to English. All relevant studies to make an update on the topic were reviewed.

IRI AND PROTECTIVE MECHANISMS OF IPC

The inflammatory cascade that is triggered by ischemia and subsequent reperfusion plays the major role in IRI. In their study Fan *et al.*[15] have demonstrated that leukocyte activation, invasion, adhesion, and impaction evidently occur in ischemic reperfusion kidney injury. This leads release of several substances and mediators such as free radicals, lysosomal enzymes and various cytokines causing cell damage, which is called IRI[16]. To overcome this tissue injury many studies suggested the IPC. Underlying mechanisms of action of the protective effect of this procedure have been studied in several trials. In their study Mahfoudh-Boussaid *et al.*[17] found that IPC reduced lipid peroxidation and showed elevated levels of endothelial nitric oxide synthase, nitrite and hypoxia inducible transcription factor-1α. Kim *et al.*[18] suggested the protective effect of isositrate dehydrogenase in IPC. Chen *et al.*[19] proposed the NF-kappa B as the key mediator for reperfusion injury and showed that IPC significantly reduced the expressions of renal adhesion molecules ICAM-1, P-selectin, and E-selectin. Fan *et al.*[15] also believed that the reduction of adhesion molecules is an important step in preventing IRI. Many other studies confirmed that the adhesion molecules have paramount importance in IRI[20,21]. In their study, Xue *et al*.[22] demonstrated the evidence that IPC mediated homing of endothelial progenitor cells played an important role in the protection of IRI. Despite all these increasing number of published studies evaluating the exact mechanisms of IRI, protective effects of IPC remains far from complete.

ANIMAL STUDIES AND CLINICAL EVIDENCE OF IPC

Since Murry *et al*.[1] described IPC in the late 1980s, several studies demonstrating its protective effects on kidney have been published. In 2012, Wever *et al*.[16] published a systematic review and meta-analysis of experimental animal studies regarding renal IPC. Serum creatinine, BUN levels and histologic changes were evaluated. They found that serum creatinine and BUN levels decreased significantly and the histologic changes were less important in the IPC group. They also performed subgroup analysis to investigate several predefined factors such as window of protection (early or late), site of preconditioning (remote and local), species (mouse or rat) and gender. In conclusion they found that IPC had persistent protective effects in all subgroups except for female experiments (only two studies). This meta-analysis indisputably demonstrates that renal IPC has protective effects to subsequent IRI, at least for small animals, since 91% of all studies were performed in rats or mice. On the flip side, there are unfortunately limited numbers of larger animal studies, with conflicting results. In a porcine model, Hernandez *et al*.[23] demonstrated that IPC had no protective effect. Yoon *et al*.[24] also demonstrated similar results. In their study on pigs, they found that IPC had no effect on serum creatinine. In contrast, levels of renal injury markers were lower in the late phase of IPC performed pigs, indicating protective effect that was not reflected in serum creatinine. Taken together, later studies suggest that the positive protective effects of IPC in small animals like rats may not be applicable to larger animal models. It seems that alternative IPC regimens need to be determined in the future.

In the light of the studies published to date, now we can talk about that IPC induces biphasic protection against IRI. Early mediators including adenosine, bradykinins, catecholamines, and opioids provide a strong, but short-lived, “classic” early protection[25,26]. While short-term mediators provide the initial protection, the activation of transcription factors and de novo protein synthesis provide a late onset, less stronger but more durable protection against ischemia called “second window of protection”[27]. The concept was previously described for cardiac IPC but it is also applicable for renal IPC[28]. In a systematic review, Wever *et al*.[16] demonstrated that second window ($\geq$ 24 h) of protection was more effective in decreasing serum creatinine after renal IRI. In their study on dogs, Kosieradzki *et al*.[29] were not able to demonstrate either early or late protective effects of IPC. But the study was performed on dogs and previous studies demonstrated that the effect of IPC in each animal species varies.

REMOTE ISCHEMIC PRECONDITIONING

In routine clinical practice the role of local IPC is very limited due to the increased risk of damage to the vascular structures. Additionally, even short-term ischemia may lead further injury in the target tissue. To avoid from the effects of local IPC the term of remote IPC is introduced, which is a more potentially clinically practical technique. This term describes the application of IPC stimulus to a remote organ e.g. a limb, which is relatively resistant to IRI. The underlying mechanisms of remote IPC are not fully demonstrated, but current concepts suggest that the protective mediators are produced secondary to the stimulus created by remote IPC. These produced mediators carry the protective effect from the site of remote IPC to the target organ[30]. It can be performed noninvasively by simply inflating and deflating a standard blood-pressure cuff placed on the upper arm or thigh to induce transient ischemia and reperfusion[31]. Most of the studies published to date demonstrated its cardiac protective effects, but there are also some studies that have revealed the potential of protective properties on kidney injury. Wever *et al*.[16] reported 30% to 60% improvement of renal protection and reduction of renal tubule damage with remote IPC. In another study, Ali *et al*.[32] found that it reduced the incidence of renal impairment. In the meta-analysis of Wever *et al*.[16], renoprotective effects of brief hind limb occlusion were reported in rats. They suggested that remote IPC has an at least equal potential for translation to clinic. In contrast with these studies, Bedir *et al*.[33] conducted a study on a porcine model, and they compared serum creatinine levels and histopathological changes. But they were unable to demonstrate any significant difference on behalf of IPC. Although large animal studies were not able to demonstrate any protective effect of both remote and local IPC against IRI, this should be interpreted cautiously before giving up this technique totally. Huang *et al*.[13] recently published a randomized, controlled study in humans, which was evaluating the effects of remote IPC. They demonstrated that lower limb IPC might reduce renal damage in patients undergoing laparoscopic partial nephrectomy.

In conclusion we can say that the positive protective effects of remote IPC on kidney injury against ischemia is limited, and its advantages are still questionable. Similar with local applications, remote IPC studies conducted in small animals have yielded encouraging results, but their applicability to humans needs further research. Unfortunately larger animal and human studies are very limited, and they have conflicting results.

IRI SECONDARY TO LAPAROSCOPIC/ROBOTIC PNEUMOPERITONEUM

Laparoscopic surgery requires adequate pneumoperitoneum throughout the surgery, but it has some well-known physiologic adverse effects on cardiac[34], pulmonary[35], and renal systems[36]. The decreased blood flow to visceral organs and increased systemic vascular resistance, which are developed secondary to increased intra-abdominal pressure are mainly responsible for these adverse effects. Additionally, the subsequent desufflation following pneumoperitoneum may lead to an IRI. Eleftheriadis *et al*.[36] were firstly able to demonstrate the increased oxidative stress in the rat liver after pneumoperitoneum. In their study, Glantzounis *et al*.[37] reported increased levels of free oxygen radicals after laparoscopic procedures, which were probably developed secondary to IRI. Akbulut *et al*.[38] firstly demonstrated the pneumoperitoneum related increased oxidative stress in kidneys.

To date lower pressure models[39,40], low-pressure pneumoperitoneum with intermittent deflation at distinct time points[41] and IPC have been attempted to reduce ischemic injury regarding pneumoperitoneum. Many human and animal studies have investigated the effects of increasing intraabdominal pressures (IAP) during laparoscopy and the benefits of low IAP. In different studies Giraudo *et al*.[39] and Samel *et al*.[40] obviously revealed that lower IAPs were related with reduced oxidative injury. But there are also some contradictory studies. In their study on rats, Yilmaz *et al*.[42] did not demonstrate any statistical significance in oxidative stress parameters at both low and high intraabdominal pressures. Polat *et al*.[43] confirmed these results in their study with human subjects. A recent study conducted by Biler *et al*.[44] clearly demonstrated that the ischemic preconditioning method should be used to reduce IRIs, rather than other low-pressure models.

ROLE OF LAPAROSCOPIC/ROBOTIC IPC

Since Murry *et al*.[1] first described the IPC, it was adopted for different laparoscopic studies. It has been proposed as an effective therapeutic approach to enhance ischemia tolerance and preserve intraabdominal organ function[3,45]. Yilmaz *et al*.[46] first demonstrated that laparoscopic preconditioning might decrease the oxidative stress in intestines following laparoscopic procedures in rats. In another study of the same group, Yilmaz *et al*.[47] demonstrated that LPC consisting of 10 min of insufflation followed by 10 min of desufflation reduced the oxidative stress that induced by long-term increased intraabdominal pressure in the plasma, liver, and kidney. But they also concluded that further studies were warranted to determine its ideal timing, before incorporating LPC to clinical applications, because the experimental protocol was too long to be applicable for the usage in humans. In the literature, different time periods for preconditioning method have been reported. However, 5- or 10-min-ischemia followed by a reperfusion of 5-10 min is used most commonly[1,48]. Arioz *et al*.[49] published a study in 2009, and compared LPC 5-min with LPC 10-min. As a result, they concluded that 5 min of pneumoperitoneum, and subsequent 5 min of desufflation, seems to be comparable to 10 min of inflation and desufflation periods, against laparoscopic IRI. So they suggested it to be more practical for clinical use[49]. It is important to mention that to date there is no human studies to assess the role of described laparoscopic/robotic IPC.

CONCLUSION

The potential positive effects of IPC against IRI have been demonstrated by several studies over the past 2 decades. Despite these encouraging findings, IPC has not been routinely used in clinical settings yet. One of the major reasons of this situation is the very limited number of larger animal and human studies and regarding conflicting results. The unknown parts of the exact mechanisms, the lack of standard protocols for its use such as clamping time, number of clamping cycles for remote IPC, using an early window or a late window, using local IPC or remote IPC, and the all remaining uncertainty regarding this process might lead clinicians to be hesitant about its clinical use. In their study in 2000, Yellon and Dana[50] asked the question: "The preconditioning phenomenon: a tool for the scientist or a clinical reality?" It is nearly passed two decades, but the same question hasn't lost its currency yet. We also agree with them and many others who made great effort on this topic that more work is needed on IRI, IPC and LPC before its adaptation to clinical settings to become something more than a tool for the scientist.

DECLARATIONS

Authors' contributions

Substantial contribution to conception and design, and acquisition of data, and analysis and interpretation of data: Zor M

Drafting the article and revising it critically for important intellectual content: Kangal KO

Giving the final approval of the version to be submitted and any revised version: Zor M

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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Mini-invasive Surgery

Case Report

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Duplicated gallbladder with obstructive jaundice: a case report with video

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Abstract

A 38-year-old male presented with painful obstructive jaundice. Ultrasound showed biliary dilatation and a duplicated gallbladder (DG). Magnetic resonance cholangiopancreatography (MRCP) imaging confirmed the diagnosis of DG and raised the suspicion of a stricture in the distal common bile duct. Endoscopic retrograde cholangiogram, sphincterotomy with small stone extraction, and biliary stent placement were accomplished, and the patient was transferred to our tertiary center. Given the report of a stricture, endoscopic retrograde cholangiopancreatography (ERCP) was repeated and showed no duct narrowing or persistent choledocholithiasis, but only one cystic duct and gallbladder filled. The patient subsequently underwent laparoscopic cholecystectomy using top-down technique with complete resection of both gallbladders. Postoperatively, the patient underwent another ERCP for elevated bilirubin due ampullary edema. Subsequently, his bilirubin normalized and he was discharged home on postoperative day 5. DG is a rare anatomical finding that may be associated with choledocholithiasis and cholecystitis. In this case, a combination of radiographic, endoscopic and laparoscopic procedures was utilized to resolve the patient's clinical problem.

Keywords: Gallbladder, duplication, cholecystectomy

INTRODUCTION

Duplicated gallbladder (DG) is an uncommon anomaly of the biliary system that may complicate the diagnosis and surgical management of symptomatic cholelithiasis[1]. Medical historians disagree about the first reported case of DG. Boyden[2] attribute the first documentation to Blasius in 1675, whereas Desolneux *et al.*[3] and Udelsman and Sugarbaker[4] both credit a sacrificial victim of Emperor Augustus

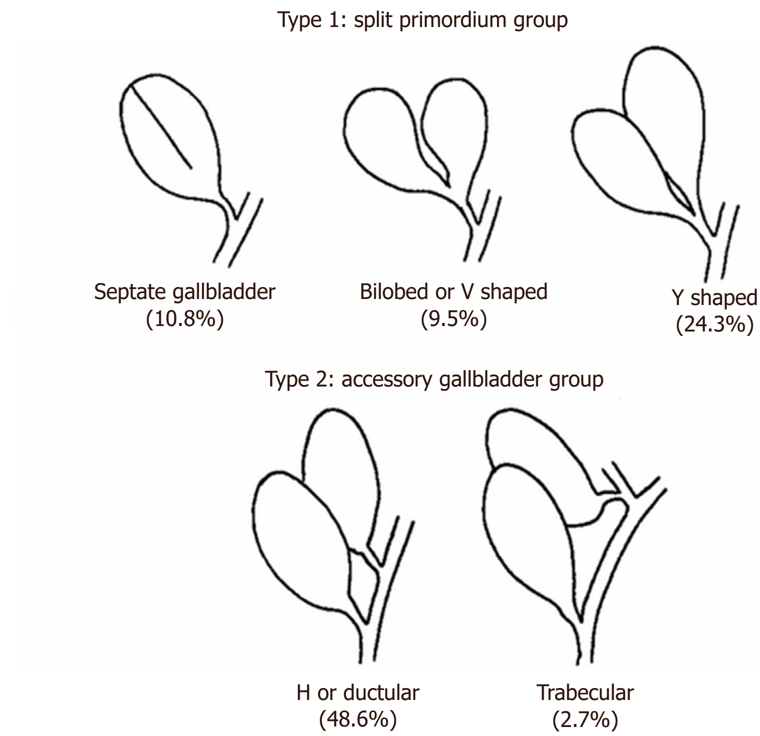

Figure 1. Types of gallbladder duplications. Adapted with permission from Harlaftis *et al.*[7], Copyright Elsevier (1977)

in 31 BC as the first reported case. There is consensus, however, over the uncommon incidence of this anomaly in the human population, which remains at 0.02 to 0.03 percent[2,5,6].

DG is thought to be the result of excessive budding of the hepatic diverticulum during the development of the biliary tree. DG and its anatomical variations were initially described in 1926 by Boyden[2]. In 1977, Harlaftis *et al.*[7] categorized duplicated gallbladder anatomy into the split primordium and accessory gallbladder groups [Figure 1]. In the type 1, or split primordium group, DGs share a common cystic duct, and are further distinguished as septated, bilobed, and Y-shaped[8]. The type 2, or accessory gallbladder group, is classified based on the presence of more than one cystic duct joining the biliary tree with two or more distinct gallbladder primordial[9]. In this group, the gallbladder closest to the liver is termed the accessory gallbladder[8]. It may be positioned under or within the liver, within the gastrohepatic ligament, or within the gallbladder fossa[9].

With respect to clinical presentation, DGs are not necessarily characterized by a specific set of symptoms[1,6,10]. Therefore, DG may be discovered preoperatively, during surgery, or during specimen processing[3]. Computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography may all result in preoperative diagnosis that assists the surgeon in planning and conducting the operation[11]. Treatment of DG via laparoscopy has been described on multiple occasions[12]. Removal of all gallbladders is vital in preventing persistent cholecystitis and future symptomatic gallstones[3,8].

CASE REPORT

A 38-year-old male presented to his local emergency department with right upper quadrant (RUQ) abdominal pain, accompanied by nausea and vomiting. A CT scan showed two gallbladders with separate cystic ducts entering distinctly into the common bile duct. There was no evidence of cholecystitis. The patient's pain resolved spontaneously and he was discharged home. Another episode of RUQ pain with nausea developed three months later, with radiation of the pain to his back. He also had jaundice, light-colored stools, and nausea. The patient again visited his local emergency department, where his bilirubin was 9.1 mg/dL. Subsequently, a RUQ ultrasound and MRCP verified duplicated gallbladder and now showed cholecystitis of the medial gallbladder. The common bile duct was dilated to 7.9 mm in diameter. An ERCP with sphincterotomy was performed and two tiny stones were retrieved. A biliary stent for stricture at the distal common bile duct was placed. The patient was transferred to our tertiary center for further management.

At our institution, a second ERCP was performed to further assess the common bile duct for a possible malignancy. In this study, no stricture was seen and the biliary stent was removed. Subsequently, he was taken to the operating room for laparoscopic cholecystectomy.

The operation was started by taking down omental adhesions and dissecting the peritoneum overlying the medial and lateral aspects of the gallbladders [Video 1]. Due to the extent of the inflammation and aberrant anatomy, a top-down dissection was then used to mobilize both gallbladders and confirm structures. During this dissection, the medial gallbladder was inadvertently entered. This decompressed the inflamed gallbladder and facilitated the rest of the operation. The cystic duct and artery of the lateral gallbladder were identified, isolated, doubly clipped and divided. Similarly, the cystic artery of the medial gallbladder was controlled. The medial cystic duct was the only remaining structure entering the gallbladder. Given the size of duct, it was divided using a stapler.

Postoperatively, the patient's bilirubin continued to rise. A third ERCP on postoperative day 1 suggested ampullary edema and intrabiliary clot without evidence of biliary injury. His bilirubin normalized gradually, and he was discharged home on postoperative day 5.

DISCUSSION

DG is not associated with specific symptoms or even with a predisposition for gallstone formation. As such, the condition may persist unnoticed or undiagnosed[6,9]. When symptoms do occur, gallbladder duplication may go unappreciated due to the rare nature of the anomaly or the insensitivity of diagnostic testing. Diagnosis of DG may be mistaken for more common problems such as folded gallbladder, pericholecystic fluid, gallbladder diverticulum, Phrygian cap, vascular band, or focal adenomyomatosis[9,13].

In the case reported herein, a preoperative CT scan and RUQ ultrasound suggested DG, which was confirmed with MRCP. It has been suggested that ERCP is the most accurate test in displaying the biliary tract anatomy of gallbladder duplications[14], however ERCP is not indicated for most patients with biliary colic due to its invasive nature[11]. In the present case, even though ERCP was performed for evaluation of the biliary stricture, it did not identify the medial gallbladder with an obstructed cystic duct. Therefore, we advocate consideration of cross-sectional imaging by CT or MRCP if RUQ ultrasound raises the possibility of gallbladder duplication.

For a surgeon without preoperative suspicion, certain intraoperative presentations of DG may be more difficult to recognize than others. Awareness of the variations is helpful. Septations and partial duplications with one cystic duct, complete duplications within a common peritoneal coat, and intrahepatic duplications may go unnoticed if the surgeon is not aware of the abnormalities[7]. When identified preoperatively or at operation, the literature suggest benefit to removal of all gallbladders at a single operation to prevent persistent or recurrent symptoms[3,8,15]. In addition, multiple pathologies may exist. Roeder *et al*.[16] reported a case of a triplicated gallbladder, where one had cholelithiasis and cholecystitis, a second had papillary adenocarcinoma, and a third was intrahepatic without disease. For these reasons, we agree a surgeon should endeavor to remove all gallbladders.

According to a growing number of case reports, cholecystectomy in the setting of gallbladder duplication may be challenging but is possible by laparoscopic approach[17-19]. Maddox and Demers[9] suggest identification of each infundibulum-cystic duct junction to permit safe laparoscopic removal. In this case, we also utilized a top-down technique via laparoscopy to verify the anatomy and safely remove both gallbladders. Laparoscopic visualization was helpful in recognizing the anatomy.

If gallbladder duplication is missed by preoperative and intraoperative assessments, persistent or future biliary symptoms are possible. In this setting, a high degree of suspicion for persistent duplicated gallbladder must be considered.

In conclusion, duplicated gallbladder is a rare anatomical finding that may be associated with cholelithiasis and cholecystitis. In this case, a combination of radiographic, endoscopic and laparoscopic procedures was utilized to resolve the patient's persistent right upper quadrant pain and jaundice.

DECLARATIONS

Authors' contributions

Literature review: Ghaderi I, Flanagan E, Bhansali S, Farrell TM
Creation of manuscript: Ghaderi I, Flanagan E, Bhansali S, Farrell TM
Video creation: Ghaderi I

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Conflicts of interest

The video was presented at American College of Surgeon Clinical Congress, Washington DC, October 2013. The authors declare that there are no conflicts of interest.

Patient consent

The report was done with patient consent.

Ethics approval

No ethics approval was needed.

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Mini-invasive Surgery

Original Article

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Laparoscopic intra-peritoneal onlay mesh plus repair for ventral abdominal wall hernias - is there substance to the hype?

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Abstract

Aim: To summarize our experience in laparoscopic intra-peritoneal onlay mesh (IPOM) plus repair for ventral abdominal wall hernias over a 10-year period.

Methods: All patients posted for laparoscopic repair of midline lower abdominal ventral hernia on an intention to treat basis were included in the study. Patients unfit for general anesthesia, patients posted for open repair or a hybrid approach (open reduction and closure of defect followed by laparoscopic IPOM repair) were excluded. Pre-operative patient demographics were noted. Intra-operative and post-operative data was recorded and analyzed.

Results: A total of 278 patients were posted for elective laparoscopic repair of lower midline ventral hernias between January 2007 and January 2017, of which, 56.1% were para-umbilical hernias and 43.9% were incisional hernias. These included 155 female patients. The average body mass index was 27 kg/m^2. Thirty-five patients were being operated for a recurrent ventral hernia. The average defect width was 1.2 cm for paraumbilical hernias and 2.2 cm for incisional hernias. The mean operating time was 55 min for para-umbilical hernias and 71 min for incisional hernias. In 13.1%, the fascia could not be sutured. There were no conversions to open surgery. Average length of hospital stay was 2.04 days with average follow-up period of 4.6 years. Overall morbidity was 7.9% with 2 recurrences. There was no mortality or mesh infection.

Conclusion: Thus, IPOM plus repair is a safe, feasible and effective technique for the treatment of ventral abdominal wall hernias.

Keywords: Laparoscopic ventral hernia repair, intra-peritoneal onlay mesh plus repair, closure of defect in the fascia, abdominal wall hernia, incisional hernia repair, para-umbilical hernia repair

INTRODUCTION

Ventral abdominal wall hernia surgery is a common procedure in the armamentarium of surgeons. The commonest forms of these surgical procedures in adults are repair of incisional hernias and surgery for paraumbilical hernia. Incisional hernias after previous abdominal surgeries occur in a varying range, reported from 11% to 20%[1-3]. Laparoscopic repair of such hernias has an advantage of shorter hospital stay, lower wound infection, earlier recovery and recurrence rates less than 5%[4-6]. Paraumbilical hernias compromise 10%-12% of abdominal wall hernias[7]. As compared to open repair, laparoscopic repair of adult paraumbilical hernias has also shown favorable outcomes[8]. Since its first description in 1993, laparoscopic repair of ventral hernias is gaining acceptance and becoming more popular by the day worldwide[9]. However, the standard laparoscopic repair of ventral hernias consisted of bridging the defect from the peritoneal side with a composite mesh, known as the intra-peritoneal onlay mesh (IPOM) repair, which is placement of the mesh in the underlay position through the laparoscopic intraperitoneal approach. Such repair is associated with a significant incidence of post-operative bulging or eventration of mesh, seromas, recurrences and non-restoration of abdominal muscle function[10-12]. To circumvent these problems, sutured closure of the defect in the fascia with intra-peritoneal mesh reinforcement has been described, termed the IPOM plus repair[13]. This repair is now the recommended procedure in the guideline of International Endohernia Society[14].

In this paper, we summarize our experience of the IPOM plus repair over a period of 10 years, beginning from January 2007 to January 2017.

METHODS

All patients posted for laparoscopic repair of midline lower abdominal ventral hernia on an intention to treat basis were included in the study. Patients unfit for general anesthesia, patients posted for open repair or a hybrid approach (open reduction and closure of defect followed by laparoscopic IPOM repair) were excluded. This approach removed patients with incarcerated, obstructed or strangulated hernias from this study as these patients were managed either by open repair or a hybrid approach. This also excluded patients with domain loss (width of the gap in fascia in resting supine position) of more than 8 cm. as these patients were electively posted for open repair prior to 2015 or given a choice of open/laparoscopic component separation reconstruction of abdominal wall after 2015.

The width of the defect was measured as the maximum distance between the medial edges of the defect in the fascia when the patient is in a resting supine position. The average defect width was 1.2 cm (range: 0.8-2.4 cm, SD 0.29 cm) for paraumbilical hernias and 2.2 cm (range: 1.0-7.5 cm, SD 0.49 cm) for incisional hernias.

The operating time was calculated from the insertion of the first trocar to exsufflation. The technical details of the surgery are briefly described. The patient was placed supine with both upper limbs by the side. The monitor was at the foot end of the operation table. The surgeon stands near the head of the patient with the camera surgeon to his left.

Ryle's tube is inserted to ensure a deflated stomach. Pneumoperitoneum is achieved by insufflating through a Veress needle inserted either below the xiphisternum, slightly to the left of the midline or at Palmer's point. Three ports are inserted [Figure 1]. Port A is optional, required only if there is adhesiolysis to be done. In such a situation, port B serves as the camera port, while port A and C are the right and left hand working ports. For suturing the defect and mesh placement, port C is the camera port while port B and D are the working ports.

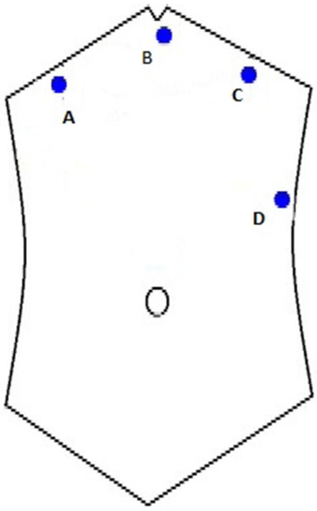

Figure 1. Port positions

Figure 2. Para-umbilical hernia after adhesiolysis

After adhesiolysis, the hernia sac is excised [Figure 2]. The defect is closed intra-corporeally with continuous sutures, using polyamide no 1 suture for para-umbilical hernia and polyamide no 1 loop for incisional hernias. The intra-peritoneal pressure may be reduced at this time to 8-10 mm of mercury to facilitate this step [Figures 3 and 4]. Composite mesh (Parietex Optimized Composite Mesh, Medtronic, USA) is introduced for intra-peritoneal placement of a size sufficient to ensure a minimum of 5 cm overlap of the edges of the defect. The mesh is first oriented with 5 transfascial sutures - 1 central and 4 peripheral, with the central sutures passed through the center of the defect to ensure proper alignment. Up to 2010, the 4 peripheral sutures were placed at the 4 corner of the mesh. However, we discovered that better alignment was obtained by placing the 4 peripheral sutures in a cross shaped pattern, along the vertical and horizontal axes of the mesh and have been doing so since then. Thereafter, interrupted intracorporeal sutures are placed at a distance of 1-1.5 cm with polyester 2-0 to complete the mesh fixation [Figure 5]. Hemostasis is ensured before desufflation.

The Ryle's tube is removed before extubation of the patient. The patients are mobilized and liquids orally are allowed once they are fully awake and non-sedated, usually 3-4 h after the surgery.

If multiple Swiss cheese types of defects are there in the fascia or the fascia is very thinned out and the fascial closure sutures tend to cut through, an IPOM repair is done. Patients are discharged after 24-48 h once they are fully mobile and comfortable on oral analgesics.

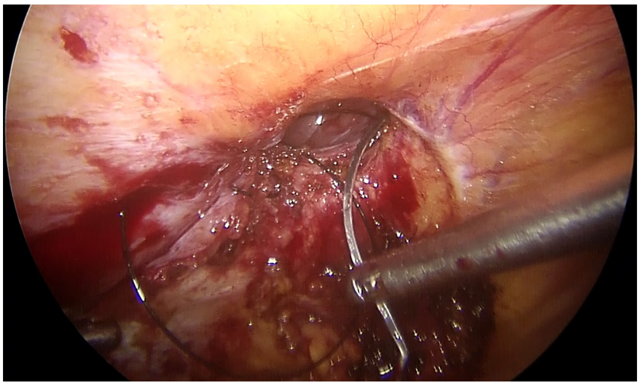

Figure 3. Intra-corporeal suturing of the fascial defect

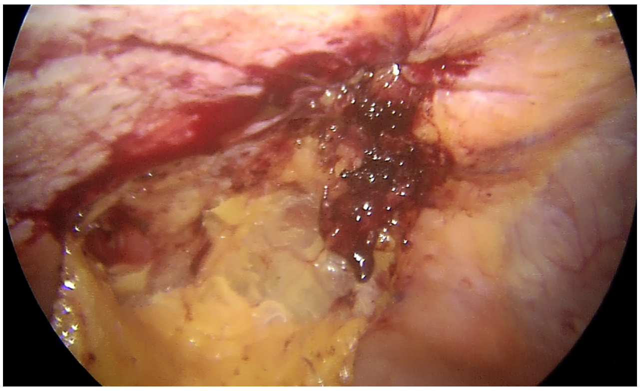

Figure 4. After closure of the fascial defect

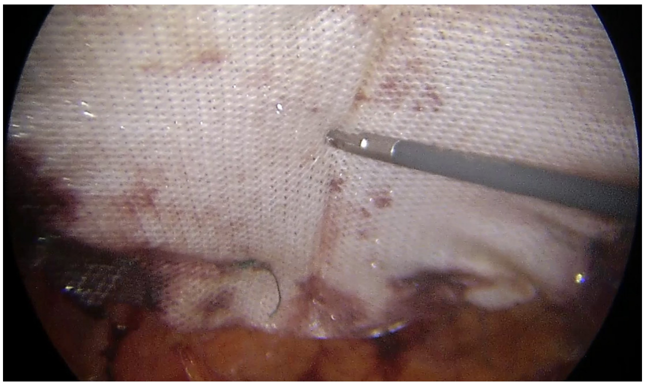

Figure 5. Intra-peritoneal onlay mesh placement and fixation

Patients are called for routine follow-up after 7 days, 1 month, 3 months, 6 months, 1 year and yearly thereafter. If patients do not physically attend their follow-up date, attempt is made to contact them telephonically. During follow-up visits, patients' complaints, if any, are noted and physical examination is done. Any suspicious bulge at the site of the previous lesion is investigated with an ultrasonography scan.

Chronic pain was defined as pain persisting at operative site beyond 6 months for which the patient needs to consume analgesic for relief.

Table 1. Patient demographics

Demographics	Data
Total number of patients in the series (*n*)	278
Male:female	123:155
Body mass index (kg/m^2)	27 (range: 21-41)
Diabetes mellitus, *n* (%)	58 (20.9%)
Smoker, *n* (%)	17 (6.1%)
COPD, *n* (%)	26 (9.4%)
Mean ASA score	2.2 (range: 1-4)

COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists

Table 2. Operative and immediate post-operative findings

Characteristics	Data
Operating time (min)	
Para-umbilical hernia	55 (range: 36-68)
Incisional hernia	71 (range: 55-105)
Conversion to open	Nil
Intra-operative bowel injury, *n* (%)	5 (1.8%)
Inability to suture the defect due to thinned out fascia (IPOM repair only) (incisional hernias), *n* (%)	16/122 (13.1%)
Length of stay (days)	2.04 (range: 1-5)

IPOM: intra-peritoneal onlay mesh

RESULTS

Between January 2007 and January 2017, a total of 278 patients were posted for elective laparoscopic repair of lower midline ventral hernias which, 156 (56.12%) were para-umbilical hernias and 122 (43.88%) were incisional hernias. Majority of incisional hernias (*n* = 94, 77.1%) were in women following either a lower segment caesarean section or hysterectomy or surgery for other gynecological pathology. In case of former two instances, though the scar on skin was Pffanensteil, the defect in the fascia was oriented in the midline vertical craniocaudal plane. Males outnumbered females in the group with para-umbilical hernias (*n* = 105, 67.3%). The patient demographics are summed up in Table 1.

A total of 35 patients had undergone prior hernia repair, of which 11 para-umbilical hernias had all suffered a failed open repair. Of these, 8 were anatomical repairs while 3 were mesh repairs. Of the 24 incisional hernias which were recurrent, 20 had undergone previous open repair while 4 had undergone laparoscopic repair. Eighteen of the open repairs and all 4 of the laparoscopic repairs had received polypropylene mesh augmentation as part of their primary repair. The width of the defect is reported separately for para-umbilical hernias and incisional hernias. In case of para-umbilical hernias, the defect ranged 1-2.5 cm, with an average of 1.2 cm. For incisional hernias, the defect width ranged 1-8 cm, with an average of 2.2 cm (SD 0.74 cm). The operative and immediate post-operative findings are summarized in Table 2.

Diligent follow-up was maintained with an average follow-up of 4.6 years (range: 1-8 years). The outcomes are summarized in Table 3.

DISCUSSION

This paper summarizes our experience in laparoscopic repair of lower midline ventral abdominal hernias with the intention of carrying out an IPOM plus repair - closure of the fascial defect with reinforcement from the peritoneal side with a composite mesh. The closure of the fascial defect has been described by various techniques - interrupted or continuous, intracorporeal or extracorporeal[15]. The extracorporeal technique consists of placing multiple stab wounds on either side of the defect to pass the suture material

Table 3. Outcomes of follow-up

Outcomes	Data, *n* (%)
Overall morbidity	22 (7.9%)
Seroma	13 (4.7%)
Chronic pain	5 (1.8%)
Recurrence	2 (0.72%)
Mesh bulge/eventration	1
Mesh infection/rejection	Nil

and take interrupted stitches[16]. This may increase the risk of suture granuloma, infection or cosmetic dissatisfaction[17]. We prefer to suture the defect intracorporeally with the knots placed extracorporeally at the two ends.

Measuring the defect preoperatively in the resting supine position allows us to select an adequately sized mesh for placement, allowing a minimum of 5 cm overlap of the edges of defect. Literature on the subject reveals that different centers select the mesh size depending on the original defect or the closed defect[16]. However the consensus is that whichever way the defect is measured, there should be an overlap over the fascial edges of the defect of at least 5 cm in all directions.

Smoking was observed in almost a fifth of our patients while co-morbidities like diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) were seen in less than 10%. COPD is a relative contra-indication for laparoscopic repair due to the possibility of retention of carbon dioxide during surgery. However, all our patients were well controlled with pre-operative bronchodilators and nebulization to minimize the risks during the immediate post-operative period. Smoking, DM and COPD are also considered as risk factors for post-operative infection and recurrence[18-20]. However, other authors do not consider them as contributory factors in recurrence after umbilical hernia repair[21]. The average BMI in our series was 27 kg/m^2, indicating that we had a larger proportion of obese patients. Obesity is a risk factor for the occurrence of incisional hernia[22] as well as recurrence after laparoscopic repair[23,24]. We reported operating times separately for para-umbilical hernias and incisional hernias as the fascial defect sizes would be different for both of these ventral midline hernias and hence, time taken for closure of defects would also be different. Our reported timings are in accordance with what is reported in literature[15,25].

Intra-operative bowel injury occurred in five of our patients. This is in keeping with the rates reported in literature[6,26]. All the patients were being operated for incisional hernia, the bowel injured was small intestine and all the injuries occurred during sharp adhesiolysis. In 4 of the patients, the injuries were seromuscular in nature while 1 was a full thickness enterotomy. All the injuries were repaired intracorporeally with 3-0 polyglactin 910 and the surgery was completed as planned. The practice of proceeding with the IPOM repair in presence of small bowel enterotomy without gross peritoneal contamination is also reported by other authors[5]. In around 13% of our patients with incisional hernias, the fascia was thinned out or there were multiple “Swiss-cheese” type of defects where the fascial sutures would not hold. Though the defect sizes would vary, we considered the hernia to be of the size of the original scar and the mesh was selected accordingly. Hence, if even a part of the original scar was intact with multiple “Swiss cheese” defects in the remaining, the entire scar was reinforced with a mesh. In these cases, we opted for a bridging repair without closure of the fascia, a practice supported by literature[27,28]. Such bridging repairs are known to give rise to post-operative bulging of the mesh, even eventration of the mesh into the defect, as seen in 1 of our patients[15,29].

Average hospital stay in our series was around 2 days. In general, laparoscopic repair is associated with a shorter hospital stay than open repairs of ventral hernias[26]. Seroma formation was seen in around 5% of our patients. The reported incidence of seroma in literature is directly proportional to the methods used to detect its presence, with the highest incidence seen when routine ultrasonography is performed for all patients[30]. The rate of this event occurring in IPOM plus is reported as 0-11.43%[15]. Its occurrence IPOM plus as compared to standard IPOM surgery is controversial as different studies have reported IPOM plus to have better outcomes[27], similar outcomes[31] or worse outcomes[32] as compared to IPOM surgery. Chronic pain, i.e., pain perceived at operative site beyond 6 months, was reported by 5 of our patients. While it has been postulated that closure of the fascia under tension may lead to higher pain perception by patients[15], Clapp *et al*.[27] reported similar rates of chronic pain after both IPOM plus and standard IPOM in their series. Two of our patients had recurrence, of which one patient had undergone an IPOM plus repair for paraumbilical hernia and the other had undergone an IPOM repair for incisional hernia. Both these patients were re-operated and an inadequately sized mesh was found to be the culprit, as after shrinkage, it had left the original defect exposed partially. In both the cases, IPOM plus repair was done laparoscopically. Literature favors IPOM plus with a lower incidence of recurrences as compared to standard IPOM surgery[32,33].

Improvement in functional status of abdominal muscles has been reported after an IPOM Plus repair. Both Den Hartog *et al*.[34] and Clapp *et al*.[27] reported improved isokinetic strength of the trunk flexor muscles and better functional activity after closure of the fascial defect. Thus, IPOM plus repair is safe, feasible and with possible advantages over a standard IPOM repair as reported in literature.

DECLARATIONS

Authors' contributions

Jani K contributed solely to the paper.

Data source and availability

The data is with the author and is available for scrutiny.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Informed consent of all patients was taken for the procedure as well as for non-indentifying inclusion in academic study.

Ethics approval

The approval of hospital ethics committee was taken for the inclusion of patients' data in the study.

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Original Article

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Pfannenstiel *vs*. midline incision for urinary diversion, following minimally invasive radical cystectomy: single center experience

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Abstract

Aim: The present study is to assess the morbidity on comparing Pfannenstiel *vs.* midline incision following minimally invasive radical cystectomy.

Methods: This is a retrospective comparative study from February 2004 to February 2017 and the number of patients studied was 116. Patients were divided into group A (Pfannenstiel incision) and group B (midline incision). The parameters analyzed were age, gender, co-morbidity, tobacco exposure, occupation, presentation, computed tomography findings, hydronephrosis, transurethral resection of bladder tumor report, duration of surgery (in minutes), hemoglobin drop (in gram per deciliter), need for blood transfusion (number of units), hospital stay (in days), epidural analgesia, analgesic requirement, pain score on first three postoperative days (on visual analogue scale), complications, and lymph node yield (numbers). Standard steps included cystectomy with bilateral pelvic lymph-adenectomy done either through the laparoscopic or robotic approach and specimen retrieval along with diversion through either Pfannenstiel or midline incision.

Results: Primary end points, post operative pain score (P = 0.0001), analgesic requirement (P = 0.0003), post operative wound complication (P = 0.002), length of hospital stay (P = 0.0003) all were less (statistically significant P < 0.05) for group A as compared to group B and secondary end points, duration of surgery (P = 0.0002), post operative paralytic ileus duration (P = 0.0006) were less (statistically significant P < 0.05) for group A as compared to group B. Other secondary end points, post operative hemoglobin drop (P = 0.08), the number of units of blood transfused (P = 0.189) and lymph node yield (P = 0.533) were comparable in either group (statistically insignificant $P \geq$ 0.05).

Conclusion: Minimally invasive (laparoscopic or robotic) radical cystectomy with an extra-corporeal diversion through Pfannenstiel incision offers an advantage of less morbidity than midline incision.

Keywords: Pfannenstiel, midline, incision, minimally invasive radical cystectomy, conduit, neobladder, morbidity

INTRODUCTION

Minimal access radical cystectomy is now commonly performed for localized carcinoma bladder but the reconstructive part of surgery is challenging. Open reconstruction can offer the advantage of minimal access surgery (MAS). Morbidity of open surgery can be reduced and the advantage of MAS can be gained with Pfannenstiel incision, transverse incisions in abdominal surgery are based on better anatomical and physiological principles[1]. In comparison with other treatment options, radical cystectomy offers better local disease control and 5-year survival.

Usually, radical cystectomy has become the part of multimodality of treatment of bladder cancer in select cases (in which neo-adjuvant chemotherapy is followed by radical cystectomy). Approaches for radical cystectomy are open, laparoscopic or robotic; and "open" approach is the gold standard of surgical treatment. Even in this era of minimally invasive surgery, there are some institutions/centers, which practice the "open" approach. Open approach has its own disadvantages like intra-operative blood loss, prolonged hospital stay, delay in recovery, significant morbidity and even mortality. But now, in the era of minimal access surgery, laparoscopy and robotic approaches can become standard of care for the surgical management of organ-confined carcinoma bladder with advantages of less blood loss, high lymph node yield, less pain, early recovery, fewer complications and mortality and short hospital stay. The major disadvantages of minimal access surgical approach are costs of implementation and lack of haptic feedback.

This study aims to assess the morbidity on comparing Pfannenstiel *vs.* midline incision for urinary diversion, following minimally invasive radical cystectomy.

METHODS

This is a retrospective comparative study from February 2004 to February 2017 and the number of patients studied was 116. Patients were divided into group A (Pfannenstiel incision) and group B (midline incision). All operations were performed by the single surgeon with experience of doing about 20 radical cystectomies per year. The incision was not allocated by any random chart or table as it is a retrospective study. The allocation was based on surgeon's preference.

We used minimal access approach for radical cystectomy. Standard steps included transperitoneal approach. 5 ports for laparoscopy and 6 ports for robotic surgery were employed. Steps were bilateral ureter dissection, posterior peritoneotomy, bilateral seminal vesicles and vas dissection, dissection of the prostate, while cystoprostatectomy specimen was freed all around, specimen bagged, followed by bilateral standard lymph node dissection and initiation of the reconstructive part. We have not used staplers for any reconstruction due to financial constraints. The procedure was completed in two stages for ileal conduit: first, pelvic lymphadenectomy with cystoprostatectomy; second, extracorporeal formation of the ileal conduit. The procedure was completed in three stages for ileal neobladder: initially, pelvic lymphadenectomy with cystoprostatectomy, secondly, extracorporeal formation of neobladder and thirdly, re-docking the robot, intra-corporeal urethro-neo-vesical anastomosis.

For reconstructive part of the procedure (either an ileal conduit or ileal neobladder), we used lower midline vertical incision (group B) or Pfannenstiel incision (group A); we divided the patients into two groups. One was with lower midline vertical incision and the other with Pfannenstiel incision. We compared

Table 1. Gender distribution of study population

	Male	Female	Total
Group A	46	7	53
Group B	57	6	63

various variables between these groups to assess the impact on outcomes. No patient was given neoadjuvant chemotherapy.

Parameters analyzed were age (in years), gender, co-morbidity, history of smoking or tobacco chewing, occupation, presentation, computed tomography findings, hydronephrosis, trans urethra resection of bladder tumor report, duration of surgery (in minutes), hemoglobin drop (in gram per deciliter), need for blood transfusion (number of units), hospital stay (in days), epidural analgesia, analgesic requirement (I.V. Tramadol was the only analgesic used, in milligrams of tramadol, no narcotic used in any patient), pain score on first three post operative days (on visual analogue scale), complications, wound complications specifically mentioned needing conservative management or secondary re-suturing (dehiscence and burst abdomen), delayed follow up, and lymph node yield (numbers). Standard steps were cystectomy with bilateral pelvic lymphadenectomy done either through the laparoscopic or robotic approach and specimen retrieval along with diversion through either Pfannenstiel or midline incision.

A midline incision begins with the vertical midline skin incision extending from pubic symphysis to just above the umbilicus; next, the sheath was opened vertically and then peritoneum was reached. A pfannenstiel incision begins with the transverse skin incision along the skin crease or 2-3 fingers above pubic symphysis extending to lateral borders of rectus muscle on either site, and then the rectus sheath was opened vertically to reach the peritoneum.

Primary endpoints in this study were postoperative pain score, analgesic requirement, postoperative wound complications, length of hospital stay and secondary endpoints were duration of surgery, postoperative paralytic ileus duration, postoperative hemoglobin drop, the number of units blood transfused, and lymph node yield.

We used a student's t-test for equality of means to compare various variables between the two groups. The analysis done was multivariate analysis.

RESULTS

The gender distribution of two groups has been shown in Table 1.

We have compared group A and group B with especial focus on various variables [Table 2]. We found that there was statistically significant ($P < 0.0006$) difference with regards to mean operative time which was 259 min for group A and 416 min for group B. This significant difference might be due to use of the midline vertical incision during initial learning curve period. The mean postoperative hemoglobin drop for group A was 1.75 g per deciliter; for group B it was 1.9 g per deciliter, which was statistically insignificant ($P = 0.08$). There was higher mean lymph node yield in group A 22.27 compared to group B which had 20.74, but it was not statistically significant ($P = 0.533$). The mean number of blood transfusions unit needed for group A (0.74) was lower than that for group B (1.00), but it was not statistically significant ($P = 0.189$).

We found that there was a statistically significant ($P = 0.000$) difference with regards to mean postoperative pain score on day 2 and day 3 between the studied groups, but the mean postoperative pain score for day 1 was insignificant for these groups. Overall there was a significantly lower pain score in group A than group B. Accordingly analgesic requirement (patients were administered injection tramadol intravenously, no additional regional/ epidural/systemic analgesia was given to any patient) was statistically significantly lower in group A as

Table 2. Comparison among the study groups for various variables

Variable	Group A	Group B	*P* value
Duration of surgery (min)	259 ± 72.14	416 ± 183.03	0.0006
Hb drop (gram per deciliter)	1.75 ± 0.71	1.9 ± 0.87	0.08
Blood transfused (units)	0.74 ± 1.01	1.00 ± 1.10	0.189
Post op pain score day-1	6.03 ± 0.27	7.9 ± 0.35	0.37
Post op pain score day-2	5.18 ± 0.99	6.0 ± 0.0	0
Post op pain score day-3	4.03 ± 0.27	5.0 ± 1.0	0
Post op pain score overall	5.08 ± 0.66	6.3 ± 0.86	0.0001
Analgesic need (milligram of tramadol)	642.45 ± 145.27	915.07 ± 137.85	0.0003
Post op ileus (days)	3.40 ± 0.96	4.61 ± 1.09	0.0006
Hospital stay (days)	10.16 ± 3.39	13.63 ± 5.37	0.004
Lymph node yield	22.27 ± 14.32	20.74 ± 13.57	0.533
Age	61.32	60.84	0.3

Table 3. Various complications among the two groups

Complication	Group A	Group B
Ileus for 3 days	42	12
Ileus for 4 days	7	17
Ileus for 5 days	3	14
Ileus for 6 days	1	1
Ileus for 7 days	0	1
Wound infection conservative management	5	13
Wound infection secondary re-suturing	3	9
Pelvic collection	1	0
Acute Respiratory Distress Syndrome (ARDS)	2	2
Pneumo-thorax	0	1
Myocardial ischemia	0	1
Acute gastric dilatation	1	0
Bowel anastomotic leak	1	0
Ureter anastomotic leak	0	3
Rectal injury (de-functioning colostomy	0	1
Death	2	3

compared to group B. It was 642.45 mg of tramadol and 915.07 mg of tramadol for group A and group B respectively, showing a significant difference (P = 0.0003).

The mean hospital stay for group A was 10.16 days and 13.16 for group B, varying significantly (P = 0.004). We have compared these two groups in relation to complications too [Tables 3 and 4]. Postoperative ileus was defined as hypo motility of the gastrointestinal tract in the absence of mechanical bowel obstruction. We have found the mean duration of postoperative paralytic ileus for group A to be 3.4 days and 4.61 days for group B; the difference was statistically significant (P = 0.001) [Table 2].

There were more wound-related complications in group B (22 out of 63 patients; 41%) than group A (6 out of 53 patients; 15%), showing a statistically significant difference (P = 0.008). As we observed, there were more overall complications in group B (30 out of 63 patients; 46%) as compared to group A (13 out of 53 patients; 24%). Complications rate was significantly higher for group B (P = 0.006).

One patient with a body mass index of 33 kg/m^2 in Pfannenstiel group had bowel leak and 3 patients of midline incision group had urine leak from the site of anastomosis, but it was statistically insignificant (P = 0.17).

We have compared mortality data between these groups and found that 2 out of 53 (3.7%) patients in group A died, while 3 out of 63 (4.7%) patients in group B died. Though there was more mortality in group B, it was not statistically significant (P = 0.47).

Table 4. Level of significance of complications among the two groups

Complications	Ileus ≤ 3 days	Ileus > 3 days	Wound infection	No wound infection	Anastomotic leak	No anastomotic leak	All complications	No complications	Death	No death
Group A	42	11	8	45	1	3	13	40	2	51
Group B	12	51	22	41	3	60	30	33	3	60
P value	0.001		0.008		0.17		0.006		0.47	

Table 5. Urinary diversion distribution of study population

	Ileal conduit	Neobladder	Total
Group A	44	9	53
Group B	44	19	63

In our retrospective study, postoperative pain score (calculated by visual analogue score) (P = 0.0001), analgesic requirement (P = 0.0003), length of hospital stay (P = 0.0004), duration of surgery (P = 0.0006), postoperative paralytic ileus duration (P = 0.0006), postoperative wound complication (P = 0.008) were less (statistically significant P < 0.05) for group A as compared to group B. But the postoperative hemoglobin drop (P = 0.08), the number of units blood transfused (P = 0.189), and lymph node yield (P = 0.533) were not significantly different statistically (comparable) among the two groups. No statistically significant difference with respect to age and gender in either group was found (P = 0.30, P = 0.57 respectively). For experienced minimal access surgeons, the ablative part of this procedure does not cause major problems but the urinary diversion part of the surgical procedure is challenging and requires more advanced laparoscopic skills[2].

DISCUSSION

Open radical cystectomy (RC) with urinary diversion (ileal conduit or ileal neobladder) has been the gold standard for treating muscle-invasive bladder malignancy[3]. Recently, minimal access approach has been adopted for radical cystectomy in performing laparoscopic RC and robotic RC. As mentioned previously, the minimally invasive approach has various advantages like magnified vision, less blood loss, minimal the postoperative pain, rapid postoperative recovery, less hospital stay and gives better cosmesis[3].

Those who have expertise in advanced laparoscopy have adopted three approaches to reconstruction:
1. Extracorporeal reconstruction through a mini-laparotomy midline or muscle-splitting incision or Pfannenstiel incision. The same incision is used for delivering the bladder specimen and lymph nodes in laparoscopic sacks. We used this approach in our study;
2. A combination of extracorporeal construction of a urinary reservoir and intra-corporeal anastomosis;
3. Complete intra-corporeal reconstruction[2].

A completely intra-corporeal procedure is a technically difficult and time-consuming procedure[4]. Manoharan *et al.*[4] described the Pfannenstiel incision for it.

As for the patients included in group A, out of 53 patients only 4 (7.5%) underwent ileal neobladder, while in group B out of 63 patients 9 underwent ileal neobladder (16.6%). All the remnant patients in either group underwent ileal conduit urinary diversion [Table 5].

Table 6 demonstrates the final histopathological T and N stage distribution of the patients under study.

In contrast to vertical incision, with Pfannenstiel incision, the whole pelvis was easily accessible, without a retractor being applied to the lateral edges[3]. Postoperative paralytic ileus duration was significantly higher in patients having lower midline incision, though we adopted the intra-peritoneal approach. The

Table 6. Final histopathology T stage and N stage of study population

Pathological stage	Number of patients
T1	16
T2	46
T3	48
T4	6
N0	78
N1	35
N2	3
N3	0

technique of robotic-assisted laparoscopic radical cystectomy and neobladder construction or conduit using a Pfannenstiel incision has been favorable. Pfannenstiel incision provides good exposure, facilitating neobladder reconstruction, can be used for specimen retrieval, bowel anastomosis and heals better with a cosmetic scar[4].

Manoharan *et al.*[4] had conducted a similar study in 2011. He showed that, for those with pfannenstiel incision the mean hemoglobin drop was 1.8 ± 1 g per deciliter, while in our study; group A Pfannenstiel incision had 1.75 g per deciliter mean hemoglobin drop. Mean operating time was 6 ± 0.8 h in their study while in our study the mean operative time for group A was 4.3 ± 1.1 h. According to what was reported by Manoharan *et al.*[4], in our study there were no intra-operative visceral injuries in group A, but in group B where midline incision was used, there was one case of rectal injury out of 63 patients (0.01%), which was managed with a de-functioning colostomy. None of the patients reported by Manoharan *et al.*[4] had positive surgical margins similar to our study with either group. The mean number of lymph nodes removed was 12 ± 3 in their study, by contrast, in our study it was 22.27± 14.32 for group A having Pfannenstiel incision. The mean hospital stay in their report was 8.5 days, but it was 10.16 ± 3.39 days in our study for group A having Pfannenstiel incision.

Raychaudhuri *et al.*[2] mentioned the work of Puppo, which was a series of laparoscopic RC with transvaginal delivery of specimens. Mini-laparotomy incision was used for the ileal conduit in that series[2]. The total operative duration was 6-9 h (in our study it was 4.3-6.9 h) and the hospital stay 7-11 days, but it was 10.16 ± 3.39 days in our study for group A having Pfannenstiel incision and for group B it was 13.63 ± 5.37 days.

Raychaudhuri *et al.*[2] also mentioned the work of Denewer who reported a series of 10 laparoscopic salvage (after radiotherapy) RC; this cohort of patients had ureterosigmoidostomy performed through a mini-laparotomy[2]. Complications (morbidity and mortality) in this study, were comparable with our study.

According to the data from an international registry on laparoscopic RC in 572 patients[3], the mean operating time was 6.2 h with only 53% having open neo-bladder. Mean operative time for group A was 4.3 ± 1.1 h and that of group B was 6.9 ± 3.0 h. Most of the midline incision cases were performed in our initial phase of minimal access approach, so we took longer time though the reconstruction time was comparable. The mean length of hospital stay as per that registry was 13 days (range 3-90 days) while in our study group B had similar length of hospital stay (13.63 ± 5.37 days) but it was mere 10.16 ± 3.39 days for group A. Intra-operative and postoperative complications occurred in 33 (7%) and 139 (28%) patients, respectively. In our study, postoperative complications for group A occurred in 24% of patients compared to the results of international registry; for group B complications occurred in 46% patients, this difference may be because we were in an initial phase learning of minimal access approach[3].

In one recent series of robotic RC, the operating time was reported to be 6.1 h[3]. With a majority of the patients having ileal conduit, the operating time for orthotopic pouch would be much more than the reported mean of 6 h. The average operating time in that series was 5 h for making an open neo-bladder without the use of surgical staplers. The shorter operating time is an important step forward in minimally invasive surgery and it would reduce the anesthesia time and the need for elective ventilation in the postoperative period.

Castillo *et al.*[5] published the complications of laparoscopic RC. Complications (morbidity and mortality) in this study, were comparable with our study, especially that of group A (Pfannenstiel incision group).

Laparoscopic RC and robotic RC provide advantages of minimally invasive surgery with better or at least equivalent outcomes in terms of cancer control. During an initial phase of learning, the operative time will be longer, but over time, there will be an apparent improvement in operational performance, thus reducing the duration of surgery[2].

Grantcharov and Rosenberg[1] observed that transverse incision offers as good an access to most intra-abdominal structures as a vertical incision. The transverse incision resulted in significantly less postoperative pain and fewer pulmonary complications. Vertical laparotomy, however, is associated with shorter operating time and better possibilities for extension of the incision. The pooled odds ratio for burst abdomen in the vertical incision group was 2.86 (95% confidence interval 1.72-4.73, P = 0.0001), in our study it was significant too (P = 0.008). Grantcharov and Rosenberg[1] concluded that transverse incisions in abdominal surgery were based on accurate anatomical and physiological principles. They should be recommended, as the early postoperative period is associated with fewer complications (pain, burst abdomen, and pulmonary morbidity). Their observations were similar to what we find in our study.

Lunacek *et al.*[6] had very positive experience with the Pfannenstiel incision approach for radical retro pubic prostatectomy. They concluded, this approach provides good exposure of surgical field wound heals well with a cosmetically acceptable scar and facilitates hernia repair through the same approach; if needed, which mimic the results of our study but their study was for an open procedure and the radical prostatectomy, rather than for cystectomy.

Smith *et al.*[7] conducted multi-institutional prospective randomized trial (RAZOR) comparing open *vs.* robotic radical cystectomy and found that estimated blood loss was significantly lower in the robotic arm, translating into significantly lower blood transfusion rates. Major complications (grade III and above) were similar in both groups. The number of lymph nodes removed was comparable. There was a trend to a shorter length of stay for robotic RC. The results were similar to the group A of our study in terms of complications, estimated blood loss, lymph node yield, and length of hospital stay.

This is a retrospective study, hence the inherent biases of the study design should be considered while interpreting the results. Our data shows we had a bias to perform neobladder with a midline incision in our initial learning curve. This fact might have skewed the data towards significantly high blood loss and duration of surgery in group B (midline incision group). This bias associated with the learning curve (rate of surgeon's progress in gaining experience) should be considered while interpreting the data.

We feel that more advanced disease may make the operation more challenging and potentially longer or with more complications. Higher stage of disease may make the procedure more challenging, but this needs further evaluation and confirmation with future studies. This study was not based on enhanced recovery after surgery (ERAS) protocol.

In conclusion, Pfannenstiel incision enhances postoperative recovery with minimal complications. It has an advantage over midline incision without compromising oncological outcomes. Pfannenstiel can be incision of choice for extra-corporeal diversion.

DECLARATIONS

Authors' contributions

Concept: Ganpule AP
Data collection, compilation: Tak GR
Manuscript writing: Tak GR, Ganpule AP
Manuscript editing: Tak GR, Ganpule AP, Singh AG, Sengar APS, Mohankumar V, Balaji SS, Sabnis RB, Desai MR

Data source and availability

Data source is available with drgopaltak@gmail.com in excel sheet form.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

As it is a retrospective study design, the ethical approval is not applicable in our hospital.

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Mini-invasive Surgery

Meta-Analysis

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Maternal and fetal delivery outcomes in pregnancies following bariatric surgery: a meta-analysis of the literature

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Abstract

Aim: The objective of this study is to evaluate maternal and fetal outcomes following pregnancies after bariatric surgery as compared to the general population affected by obesity.

Methods: A systematic review was conducted through MEDLINE, Cochrane, and EMBASE to identify relevant studies from 2007 to 2016 with comparative data on the maternal and fetal delivery outcomes following bariatric surgery as compared to the population affected by obesity. The primary outcome analyzed was the rate of cesarean deliveries. Other outcomes included intrauterine growth restriction, small for gestational age, large for gestational age, macrosomia pregnancy-induced hypertension, gestational diabetes, assisted vaginal delivery, and preterm delivery. Statistical analysis was done using fixed-effects meta-analysis to compare the mean value of the two groups (Comprehensive Meta-Analysis Version 3.3.070 software; Biostat Inc., Englewood, NJ).

Results: Out of 549 studies, 13 were quantitatively assessed and included for meta-analysis. The need for caesarean sections in post-bariatric women was found to be significantly lower when compared to women affected by obesity [odds ratio (OR) 0.623, $P < 0.001$). There were also significant reduction in the incidence of LGA (OR 0.491, $P < 0.001$), macrosomia (OR 0.251, $P < 0.001$), and assisted vaginal delivery (OR 0.807, $P < 0.001$) in the post bariatric group of women. There was an increase in the incidence of PIH (OR 1.113, $P < 0.001$), SGA (OR 2.305, $P < 0.001$) and IUGR (OR 2.099, $P < 0.001$). The incidence of preterm delivery (OR 0.982, $P > 0.05$) and gestational diabetes (OR 1.046, $P > 0.05$) were similar in both groups.

Conclusion: Patients affected by obesity considering conceiving in the near future should consider bariatric surgery prior to conception to lower their risk of potentially adverse delivery outcomes.

Keywords: Bariatric, pregnancy, neonatal, maternal

INTRODUCTION

Currently in the United States, more than two-thirds of the adult population is overweight and one-third are obese[1,2]. The most widely accepted measure used to define obesity is a body mass index [BMI; weight (kg)/height (m^2)] of more than 30 kg/m^2, as recommended by the National Heart, Lung and Blood Institute's North American Association for the Study of Obesity[3].

In general, being obese carries increased health risks for the individual. Serious health consequences associated with obesity include type 2 diabetes, osteoarthritis, heart disease, stroke, and certain cancers[4]. More specifically, obesity in women of childbearing age is associated with subfertility/infertility due to increased rates of anovulation[5,6]. Pregnancy associated complication rates are also increased in obese women, including gestational diabetes, preeclampsia, cesarean delivery, and infectious morbidity[5,7].

The neonate of a mother who is obese is also at increased risk for complications. While studies have not found higher incidence of spontaneous preterm labor, there are increased rates of preterm delivery for maternal or fetal indications[8]. In addition, studies have found an increase in macrosomic and large for gestational age (LGA) infants among mothers who are obese[9]. Finally, there are multiple congenital obesity-related abnormalities such as neural tube defects, cardiac anomalies and facial clefting as well as increased risks with miscarriage and stillbirth[9].

Weight loss outside of pregnancy, whether achieved via surgical or nonsurgical methods, has been shown to be the most effective intervention to improve medical comorbidities, especially diabetes and hypertension. Nonsurgical approaches to weight loss include diet, exercise, behavioral changes, and pharmacotherapy. However, bariatric surgery has been found to be both a clinically and cost-effective intervention for people affected by obesity as compared to the nonsurgical approaches[4]. There are several bariatric procedures available to qualifying patients, with the four most common being: adjustable gastric band, laparoscopic sleeve gastrectomy, gastric bypass, and biliopancreatic diversion with duodenal switch.

While there have been several studies on the effects of obesity on maternal and fetal outcomes, there have only been a few systematic reviews looking at these outcomes in patients that have undergone bariatric surgery[10-12]. However, multiple papers have been published in the last few years to further explore the topic. Our goal in this systematic review is to compare maternal and neonatal outcomes in patients who are obese that have undergone bariatric surgery and those that have not.

METHODS

A systematic review was conducted through MEDLINE, Cochrane, and EMBASE to identify relevant studies from 2007 to 2016 with comparative data on the maternal and fetal delivery outcomes following bariatric surgery as compared to the population affected by obesity. The following terms were searched: pregnancy outcomes AND bariatric surgery, neonatal outcomes AND bariatric surgery, maternal outcomes AND bariatric surgery, delivery outcomes AND bariatric surgery and perinatal outcomes AND bariatric surgery. The following outcomes were recorded: (1) the primary outcome was rate of cesarean delivery; (2) the secondary outcomes included small for gestational age (SGA) or < 10% of birthweight as compared to infants of same gestational age, LGA or > 90% of birthweight as compared to infants of same gestational age, macrosomia (> 4000 g at birth), assisted vaginal delivery, and preterm delivery (< 37 weeks gestational age at delivery).

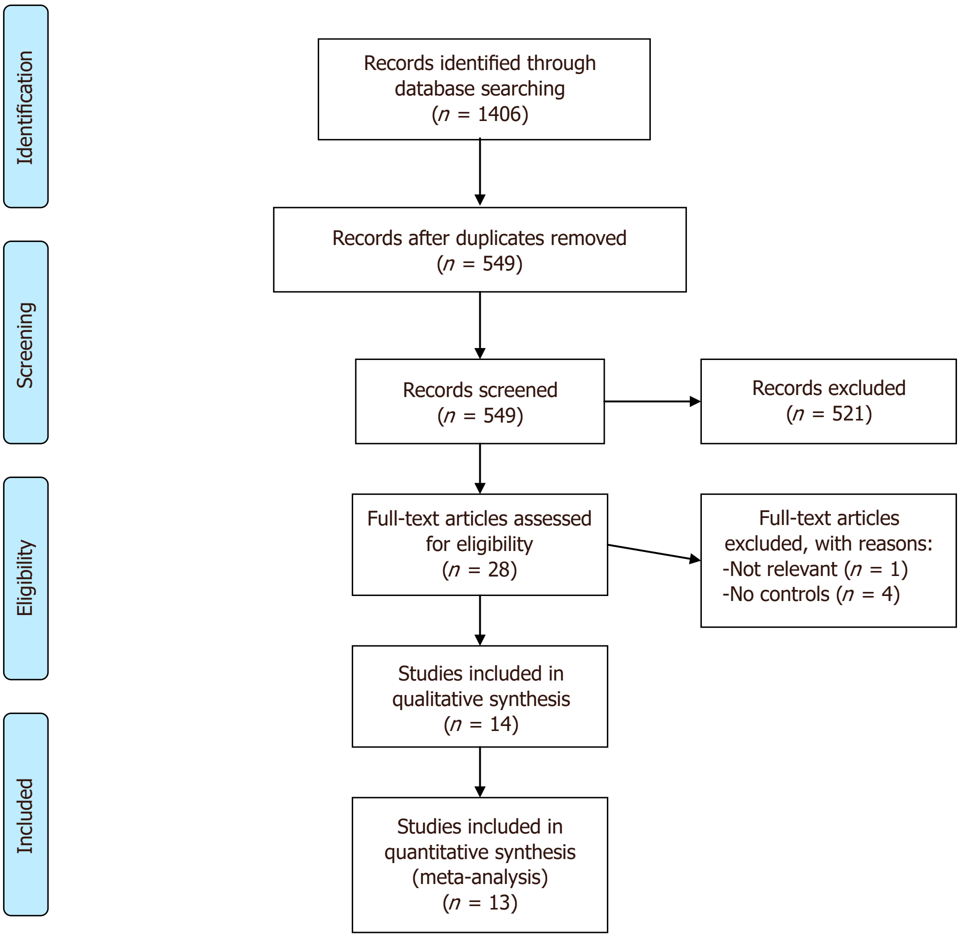

Figure 1. PRISMA flow diagram

Cohort studies that reported on fetal and/or maternal outcomes in terms of the comparison of women who are obese that underwent bariatric surgery to women affected by obesity who did not have bariatric surgery were included with obese being defined as a BMI ≥ 30. For our purposes, bariatric surgery included any weight loss surgery. Papers selected were published in English or able to be translated into English. Papers were also selected based on the ability to directly compare data as presented. Studies were excluded if they did not have a control population or included non-obese women in the study.

The Newcastle-Ottawa scale was used by two assessors to evaluate the quality of the studies based on selection, comparability and outcome. Only studies found to have a 9 or greater points (from a maximum of 10 points) were selected for analysis [Figure 1].

The results are expressed as standard difference in means with standard error. Statistical analysis was done using fixed-effects meta-analysis to compare the mean value of the two groups (Comprehensive Meta-Analysis Version 3.3.070 software; Biostat Inc., Englewood, NJ).

RESULTS

Search results

The electronic search from 2007 to 2016 yielded a total of 549 individual titles, of which 28 were found to be potentially relevant based on abstract. After a full text review of the 28 studies, a total of 13 were determined by the Newcastle-Ottawa scale to be relevant[13-25].

Table 1. Selected studies

Author	Year	Country	Size
Lapolla *et al.*[13]	2010	USA	120/83
Abenhaim *et al.*[14]	2016	USA	221,580/9587
Adams *et al.*[15]	2015	USA	10,447/2666
Amsalem *et al.*[16]	2014	Israel	109/109
Aricha-Tamir *et al.*[17]	2012	Israel	144/144
Berlac *et al.*[18]	2014	Denmark	826/415
Ducarme *et al.*[19]	2007	France	414/13
Johannsson *et al.*[20]	2015	Sweden	2356/596
Kjaer *et al.*[21]	2013	Sweden	1277/339
Parker *et al.*[22]	2016	USA	185,120/1585
Patel *et al.*[23]	2008	USA	43/26
Santulli *et al.*[24]	2010	France	120/24
Stephanson *et al.*[25]	2016	Sweden	447/163

Of the 13 studies, 5 were from the USA, 3 were from Sweden, 2 were from France, 2 were from Israel, and 1 was from Denmark. All studies included obese controls as well as post-surgical women who are obese and were published within the last 10 years [Table 1].

Primary outcomes

The primary outcome of cesarean section rates included 10 papers[13,14,16-19,21-24] and had 230,994 women in the control population and 5571 women in the post-surgical population. As compared to the control population, there was a decrease in the rates of cesarean sections found among the post-surgical population [odds ratio (OR) 0.623, 95% confidence interval (CI) 0.600-0.646, P = 0.000] [Figure 2].

Secondary outcomes

The secondary outcomes evaluated included: pregnancy-induced hypertension (PIH), gestational diabetes (GD), intra-uterine growth restriction (IUGR), SGA, LGA, macrosomia, assisted delivery, and premature delivery.

The PIH review included 8 papers[13,14,16,18,19,22-24] and had 89,952 women in the control population and 3094 women in the post-surgical population. As compared to the control population, there was an increase in the rates of PIH in the post-surgical population (OR 1.113, 95% CI 1.067-1.161, P = 0.000) [Figure 3].

The GD review included 9 papers[13,14,16,18-23] and had 57,939 women in the control population and 1217 women in the post-surgical population. As compared to the control population, there was no difference in the rates of gestational diabetes in the two groups of patients (OR 1.046, 95% CI 0.984-1.112, P = 0.145) [Figure 4].

The IUGR review included 5 papers[14,16,22-24] and had 8357 women in the control population and 452 women in the post-surgical population. As compared to the control population, there was an increase in the rates of IUGR in the post-surgical population (OR 2.099, 95% CI, 1.904-2.315, P = 0.000) [Figure 5].

The SGA neonates review included 6 papers[13,15,19-21,23] and had 816 women in the control population and 428 women in the post-surgical population. As compared to the control population, there was an increase in the rates of Small for Gestational Age neonates in the post-surgical population (OR 2.305, 95% CI 2.036-2.611, P = 0.000) [Figure 6].

The LGA review included 5 papers[13,15,20-22] and had 15,869 women in the control population and 412 women in the post-surgical population. As compared to the control population, there was a reduction in the rates of LGA babies found in the post-surgical population (OR 0.491, 95% CI 0.441-0.547, P = 0.000) [Figure 7].

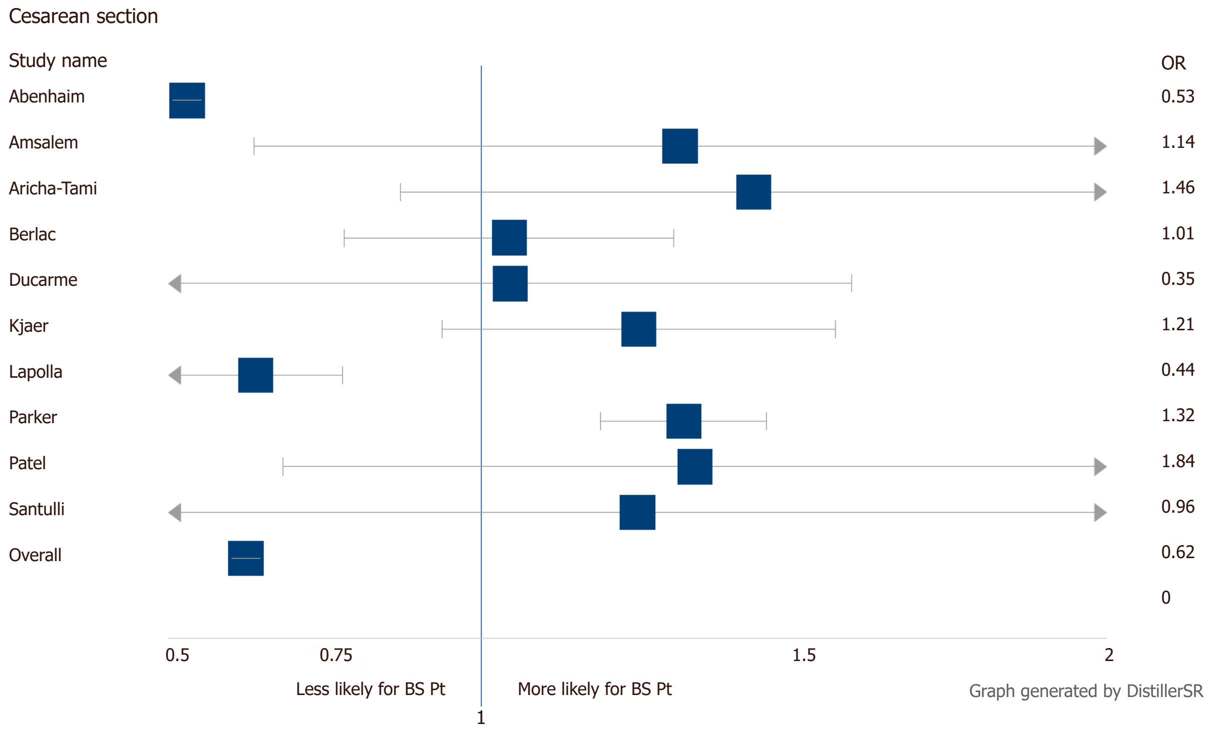

Figure 2. Incidence of cesarean section

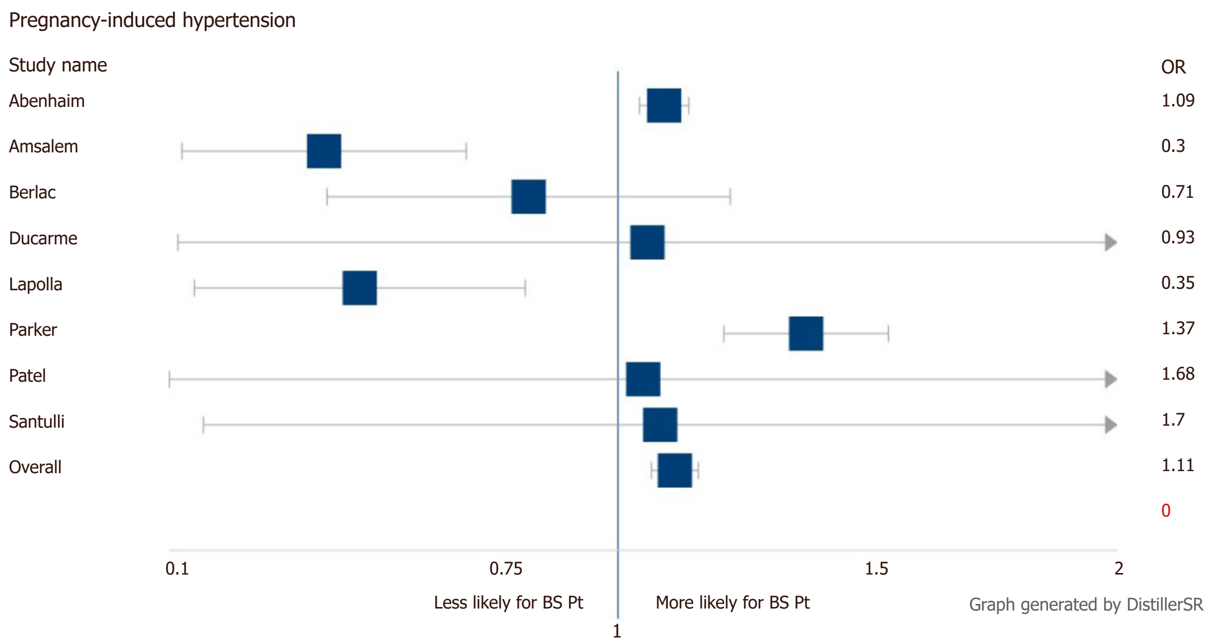

Figure 3. Pregnancy induced hypertension

The macrosomia review included 8 papers[13-17,19,20,23] and had 17,209 women in the control population and 312 women in the post-surgical population. As compared to the control population, there was a reduction in the rates of macrosomia found among the post-surgical population (OR 0.251, 95% CI 0.223-0.281, P = 0.000) [Figure 8].

Young et al. Mini-invasive Surg 2018;2:16 I http://dx.doi.org/10.20517/2574-1225.2017.50

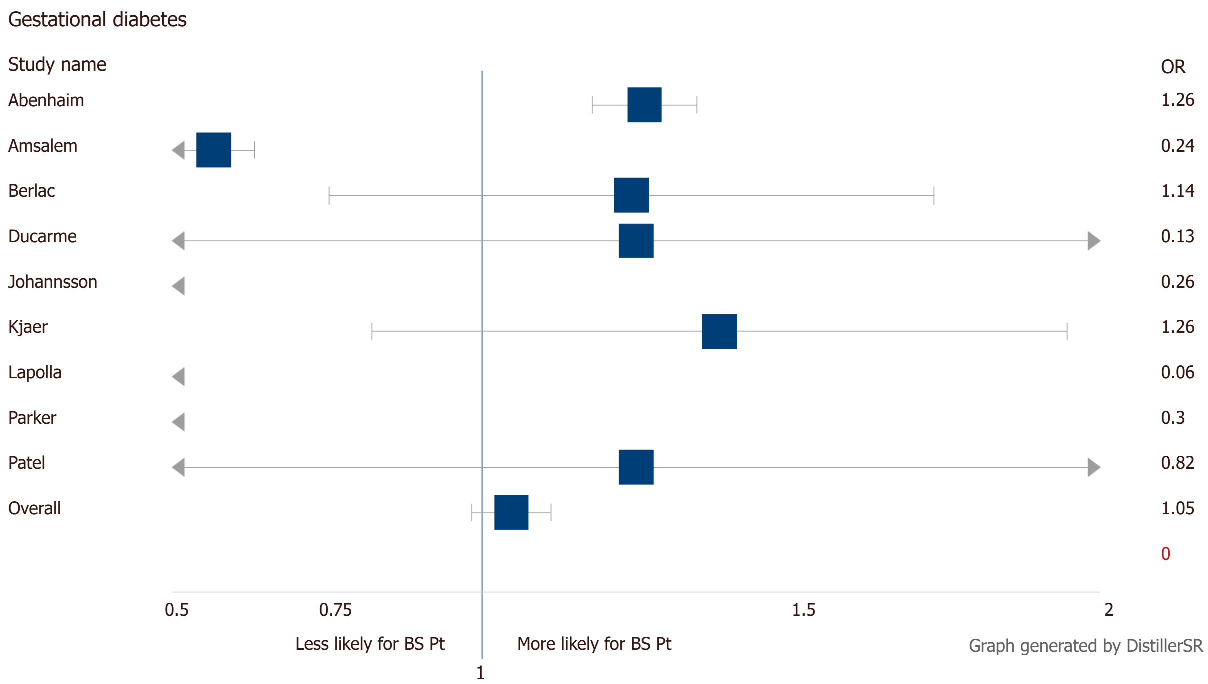

Figure 4. Gestational diabetes

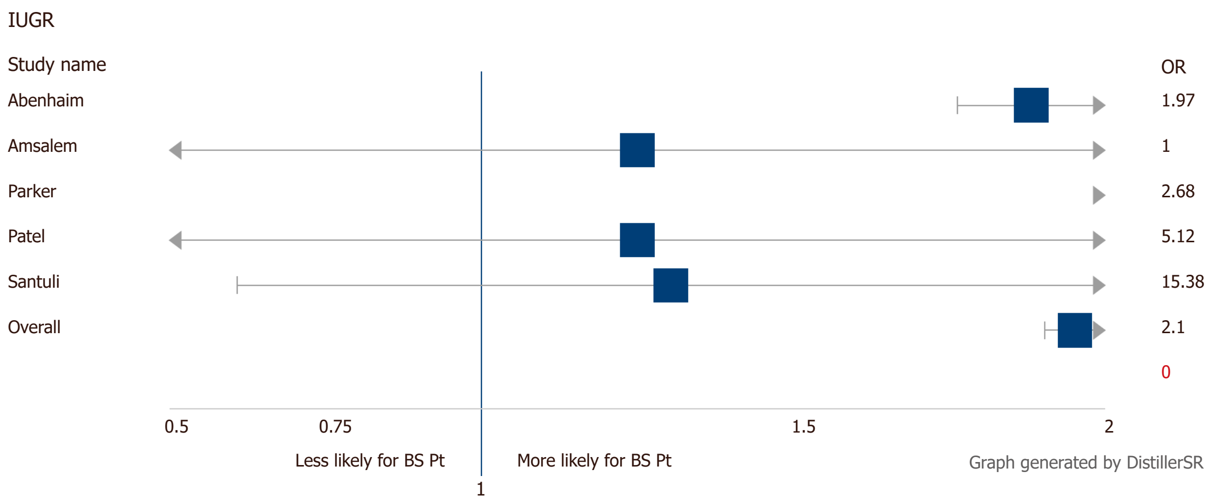

Figure 5. Intra-uterine growth restriction

The assisted delivery review included 7 papers[14,17-19,22-24] and had 16,574 women in the control population and 298 women in the post-surgical population. As compared to the control population, there was a reduction in the rates of assisted deliveries in the post-surgical population (OR 0.807, 95% CI 0.717-0.917, P = 0.000) [Figure 9].

The premature delivery review included 9 papers[13,14,16,19-21,23-25] and had 19,963 women in the control population and 1051 women in the post-surgical population. As compared to the control population, there was no difference in the rates of Premature Delivery found in the post-surgical population (OR 0.982, 95% CI 0.918-1.050, P = 0.591) [Figure 10].

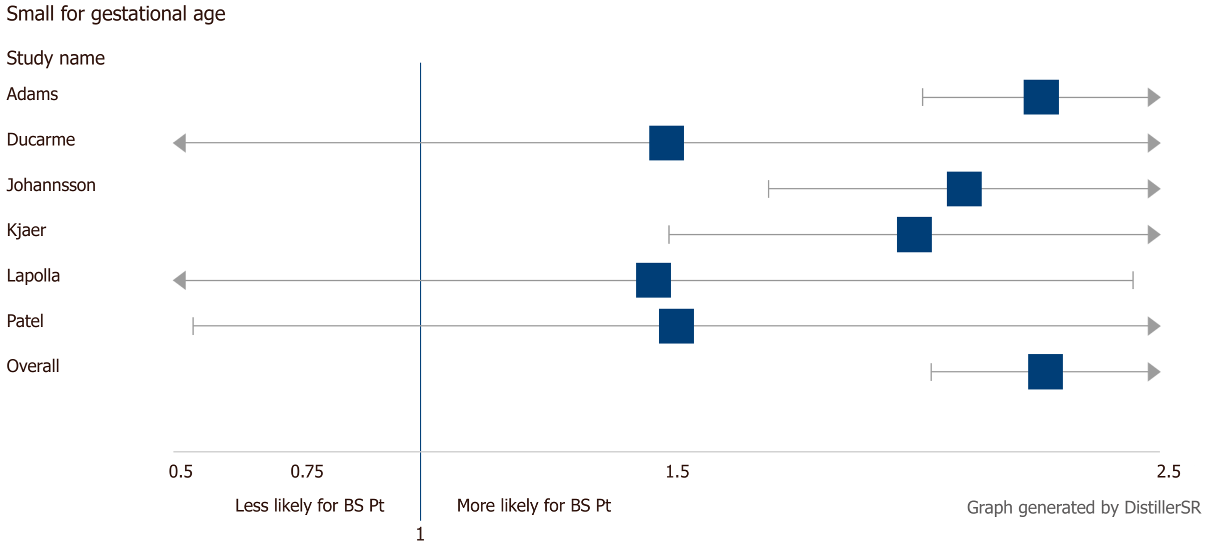

Figure 6. Small for gestational age

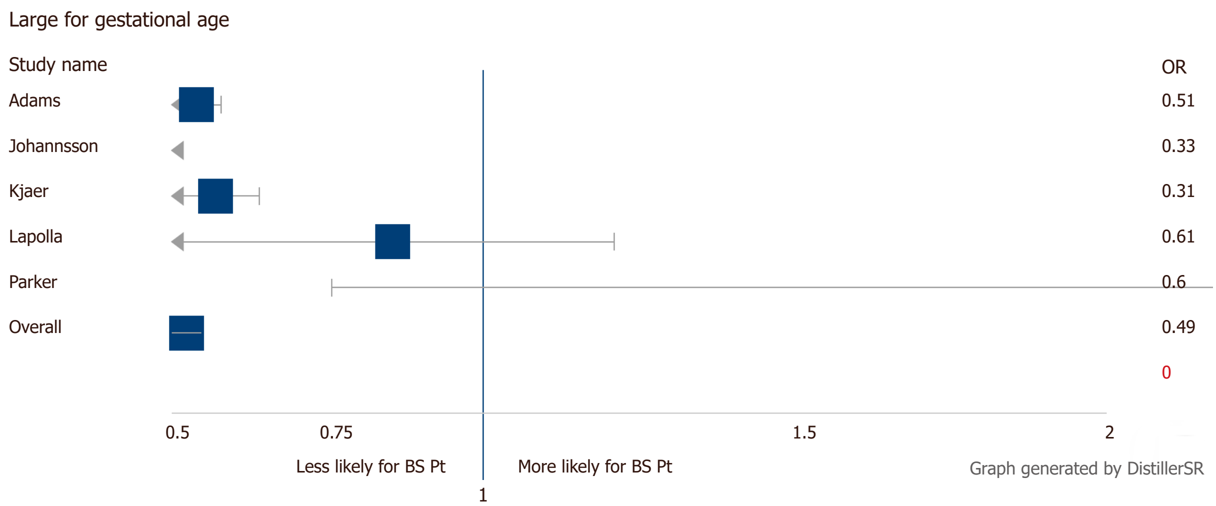

Figure 7. Large for gestational age

DISCUSSION

Main findings

Our findings in this meta-analysis are that women affected by obesity who undergo bariatric surgery have a decreased incidence of cesarean section, assisted delivery, LGA and macrosomic neonates as compared to obese controls. In addition, there was an increased incidence of pregnancy-induced hypertension and SGA and IUGR neonates in the post-surgical candidates. There was no difference in the incidence of gestational diabetes or premature delivery in these two groups.

Cesarean section

Previous systematic reviews have shown inconsistent results in cesarean section rates after bariatric surgery[10-12]. Vrebosch *et al.*[10] found a lower incidence of C-sections while both Galazis *et al.*[11] and Yi *et al.*[12] found no difference.

In the 10 studies used for this review, there was a large variation in their results[13,14,16-19,21-24]. One study found surgery as an independent risk factor[22] while two studies found a decreased rate of C-sections among the

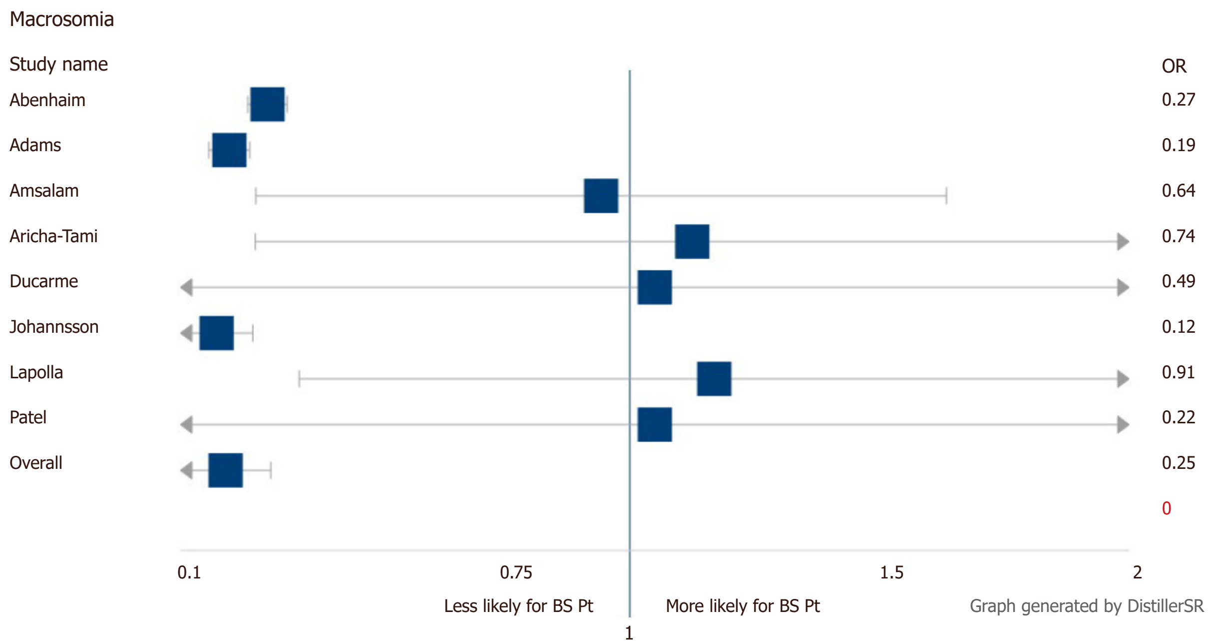

Figure 8. Macrosomia

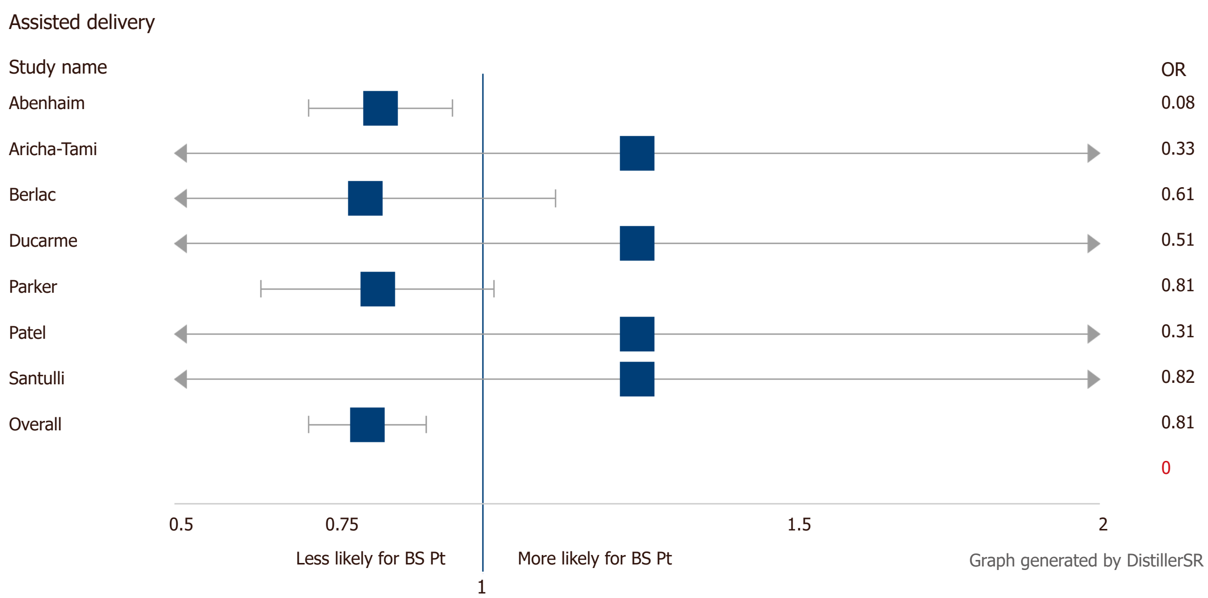

Figure 9. Assisted delivery

event group[13,14]. The remaining seven studies did not find a difference between the two groups. However, bariatric surgery reduces leptin, a hormone increased in maternal obesity that is noted to have a tocolytic effect on the myometrium theorized to prolong labor and increase the likelihood of cesarean. Therefore, post-bariatric women who are obese may produce less leptin resulting in better contractility compared to the obese control.

Our analysis found there was a decreased incidence of cesarean sections in the bariatric surgical women affected by obesity, as compared to the obese controls. We conclude that bariatric surgery lowers the rate of cesarean deliveries.

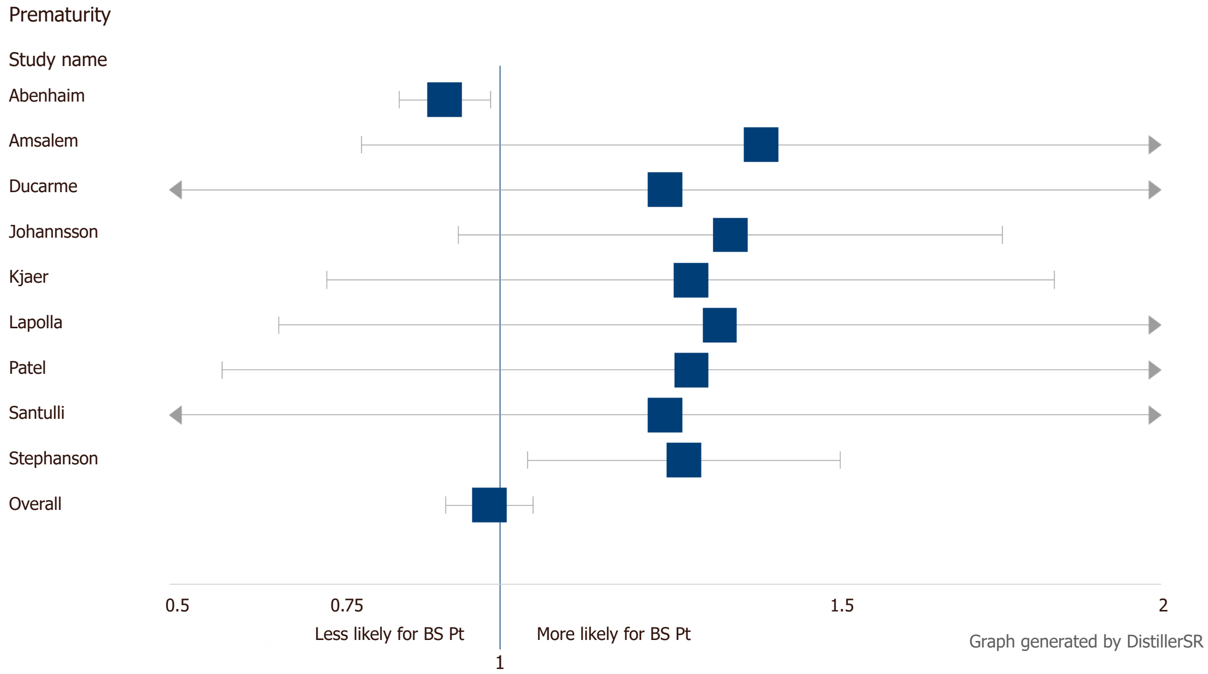

Figure 10. Premature delivery

PIH

There was variation among the 8 studies used in this analysis[13,14,16,18,19,22-24]. While the majority of the studies showed no difference in the two groups, Parker *et al.*[22] showed an increase in PIH. Parker *et al.*[22] theorized this is likely due to the fact that the average bariatric candidate is white and older which pre-disposes them to hypertension.

GD

Prior systematic reviews have shown either a decrease or no change in the rates of GD among the bariatric surgery patient[10-12]. The 9 studies used in this review are no exception[13,14,16,18-23]. While there were 4 papers showing a decrease in the rates of GD[13,16,20,22], the majority did not show a difference. It has been theorized that there is a reduction in the rates of GD after bariatric surgery due to absorption or metabolic changes[24]. However, our data did not show a difference in the rates of GD between the two groups. This is likely due to the metabolic changes associated with prolonged obesity and is not related to surgery.

IUGR

Five studies were included in our review of IUGR rates in respect to bariatric surgery[14,16,22-24]. Individually, they found either no difference or an increased rate of IUGR among the bariatric surgical patient as compared to their control. In analyzing the five studies together, we concluded there was an increased rate of IUGR in association with bariatric surgery.

The explanation for this finding remains unknown. It has been theorized that malabsorption and nutritional deficiencies during the pregnancy may lead to the growth restriction; however fetal growth restriction has many etiologies including aneuploidy, infection, and congenital malformations[23]. Both malabsorption and nutritional deficiencies are more often associated with gastric bypass procedures rather than the banding procedure. A sub analysis to compare the two procedures was not able to be performed as two of the studies only included the Roux-en-Y bypass[23,24] while the other three did not specify the surgical procedure performed. Further studies would need to be performed to determine the IUGR rates in bypass versus banding patients.

SGA

The 6 studies included in this section found either no difference or an increased risk of SGA neonates among bariatric surgery patients[13,15,19-21,23] while our data suggests an increased risk of SGA among the bariatric surgery woman as compared to the controls. However, this is potentially due to the same reasons as listed above for IUGR.

Of the six studies reviewed, only two specified the banding procedure for their surgical subjects[13,19]. A sub analysis of this data showed no difference in the surgical patient versus the control when banding is performed, thus giving us indeterminate results for this category. Further studies would need to be to determine the SGA rates in bypass versus banding patients.

LGA and macrosomia

A total of 5 studies included data on LGA[13,15,20-22] and 8 studies included data on macrosomia rates[13-17,19,20,23]. While there were a few select papers that showed no difference, the majority of the studies reviewed showed a significant decrease in the rates of both LGA and macrosomic neonates in the bariatric surgery patient. Women who gain less weight during the pregnancy, on average, have a decreased chance of delivering a LGA or macrosomic neonate[15].

Our analysis found there was a decreased incidence of both LGA and macrosomia in the bariatric surgical women who are obese, as compared to the obese controls. We conclude that bariatric surgery lowers the rates of LGA and macrosomic neonates.

Assisted delivery

The majority of the 7 papers included in this section showed no difference for bariatric surgery patients[14,17-19,22-24]. However, when we ran the data combined we found a decreased rate in assisted delivery as compared to the obese control group. This is likely due to a decrease in the size of the neonate in the bariatric surgery patient.

Premature delivery

None of the 9 studies included showed a difference in the rates of premature delivery of the neonate[13,14,16,19-21,23-25] and our data supports this conclusion. We did not find any significant difference in the bariatric surgery patient and thus cannot associate surgery to the incidence of early delivery rates.

Strengths and weaknesses

This is the most recent systematic review on the subject of bariatric surgery and maternal and neonatal outcomes. This was done on a large data size including a total of 439,561 subjects. We used a total of 13 studies in order to give a comprehensive and unbiased review of the current material. Time between surgery and pregnancy was not able to be included as only four of the articles included this variable. In the future, the inclusion of miscarriage rates associated with bariatric surgery and a more extensive review of maternal complications compared with time between surgery and pregnancy would further evaluate the fetal and maternal outcomes in post-bariatric surgical patients.

However, there are always limitations to every review. We only included papers that were published in English or were able to be translated into English. In addition, not all of the studies separated the various types of surgery so we could only review bariatric surgery as a whole. Finally, while we used the BMI range of “obese” there was some variation in the obese range between the controls and bariatric surgery patients.

DECLARATIONS

Authors’ contributions

Primary author: Young B

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Availability of data and materials
Data are available on request.

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All authors declare that there are no conflicts of interest.

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Not applicable.

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Mini-invasive Surgery

Review

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The treatment of early rectal cancer in the era of adjuvant and neo-adjuvant therapy

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Abstract

The accurate staging of rectal cancer improves the stratification of patients for adjuvant therapy. Staging of tumor with endoluminal ultrasonography (EUS) shows a good correlation with histology (κ = 0.85; 95% confidence interval 0.76-0.95). Overall pT and pN stage accuracy of EUS was 92% and 65% respectively. The staging of local disease can be further augmented by EUS guided fine needle aspiration of extra rectal lesions lying within or outside of the mesorectum. In a systematic review of local excision after neoadjuvant therapy a total of 22 unique studies reporting on 1068 patients were analysed. At a median follow-up of 54 months, ypT0 tumours had a pooled local recurrence rate of 4% and a median disease-free survival rate of 95%. Outcomes for $\geq$ ypT1 tumours were much worse with pooled local recurrence and disease-free survival of 22% and 68%, respectively. In a review of 22 studies, 804 patients who underwent local excision followed by adjuvant therapy either for unfavourable histology, prohibitive comorbidity or patient choice. the pooled local recurrence was 5.8% for pT1 tumours, 13.8% for pT2 tumours and 33.7% for pT3 tumours. In addition, the response to radiotherapy may be enhanced by aspirin, metformin and statins.

Keywords: Early rectal cancer, local excision, neoadjuvant chemoradiotherapy

BACKGROUND

The treatment of rectal cancer has advanced considerably during the last 30 years. It is widely accepted that surgery should be based on sound oncological principles where the aim is to completely excise the surrounding mesorectum in order to achieve a resection margin free from microscopic disease, together with an adequate lymph node harvest. Commonly referred to as total mesorectal excision (TME), this technique in combination with accurate post-operative staging has improved the oncological results of surgery[1-3]. Nevertheless, the debate with regards to the necessity to completely remove the mesorectum in the setting of early rectal cancer is still not fully resolved. What is clear from the evidence is that involvement of the circumferential resection margin (CRM) remains one of the most powerful predictors of local recurrence in rectal cancer.

The Swedish Rectal Cancer and Dutch TME trials gave credence to the concept that local control could be enhanced by the addition of neoadjuvant short course radiotherapy (SCRT)[3,4]. Indeed, the National Institute of Clinical Excellence in the United Kingdom currently recommends that neoadjuvant treatment is administered in the form of SCRT for moderate-risk tumours (cT3b or greater or suspected nodal involvement or venous invasion) and as long course chemoradiotherapy (LCCRT) for high-risk tumours that either threaten the circumferential resection margin or encroach on the levator plate[5]. Radical surgery remains the cornerstone of treatment for locally advanced rectal cancer with 5-year local recurrence (LR) and disease-free survival rates of 4% and 86%, respectively[1,2], and a 30-day mortality rate of 0.9%-1.5%[4,6-8]. The down side of radical surgery is that, even in experienced hands, morbidity occurs in 38%-54% of patients[4,6-8] and is associated with a significant adverse impact on quality of life with elevated levels of bowel, urinary, and sexual dysfunction[9-12]. In addition, there is a perception in the UK that local control is enhanced in disease that threatens the mesorectal rectal fascia with the use of LCCRT. Moreover, the use of LCCRT may result in a pathological complete response (pCR) in 15% to 25% of cases with contemporary neoadjuvant LCCRT regimens[13-15]. This has led to the concept of watchful waiting, the success of which is clearly dependent on the accurate prediction of a complete clinical response (cCR) and does not necessarily correspond to a pCR. Of note, in a pooled analysis of neoadjuvant treatment studies, cCR was associated with pCR in only 30% of patients[16]. It is noteworthy, however, that a pCR is heavily dependent on the quality of the surgical specimen received and the accuracy of pathological examination, which may vary considerably[17,18].

In view of the downstaging effect of LCCRT and the potential to obtain a pCR, there is increasing evidence to suggest that patients with pCR could be safely managed by local excision. Local procedures, such as transanal endoscopic microsurgery (TEM), which was first described in the 1980s, and more recently, transanal endoscopic operation (TEO) and transanal minimally invasive surgery (TAMIS), can potentially avoid the morbidity associated with radical surgery and enable organ preservation[19]. A recent systematic review by our own group suggested that local excision after neoadjuvant therapy for rectal cancer should only be considered as curative, with an acceptable level of local control, if a pCR was obtained. Pooled local recurrence rates were significantly greater and median disease-free survival significantly lower among tumours staged as ypT1 or above compared to ypT0 tumours[20]. In this article we describe our approach to the management of early rectal cancer, its staging and our evidence-based rationale for the use of neoadjuvant and adjuvant therapies.

STAGING EARLY RECTAL CANCER

The accurate staging of colorectal neoplasia can improve the stratification of patients for adjuvant treatment. We strongly believe that endoluminal ultrasound is a powerful tool in staging early disease. In support of this view, our initial work focussed on predicting the mural extent of neoplasia. Colonoscopic endoluminal ultrasonography (EUS) was used in a prospective study to determine the stage of rectosigmoid neoplasia in 121 patients. Mural tumour (T) stage was designated by EUS as uT0/1-uT4 in 121 patients. Specific nodal (N) staging was performed in 39 of these cases. EUS staging was compared with histological stage (pT and pN) in 93 patients who underwent resection. Mural staging of disease using colonoscopic EUS showed good correlation with histopathological stage (κ = 0.85; 95% confidence interval 0.76-0.95). Overall pT and pN stage accuracy of EUS was 92% and 65% respectively[21].

In a later study, the accuracy of colonoscopic EUS was assessed in the selection of patients with rectal neoplasia suitable for local excision by TEM. Patients with premalignant (uT0) lesions or with uT1 tumours that had favourable histology were offered a TEM. This has been our preferred method of local excision since 1996. Data were collected prospectively over a six-year period. The preoperative stage predicted by EUS (uT stage) was compared to the postoperative histopathological stage of the resected specimens (pT stage). One hundred and fifty-six EUS examinations were evaluated. Sixty-two patients went on to have TEM whilst the remaining 94 had another form of surgery. Of the 62 patients undergoing TEM, 3 were over staged on EUS. No patients were understaged, giving an accuracy of 95%. The accuracy of EUS at predicting more advanced disease fell to 89%, giving an overall accuracy of 92%[22]. Indeed, we feel that EUS in our institution is highly accurate at predicting T0/1 *vs*. T2 disease and we routinely use EUS in combination with CT and MRI before planning intervention. In addition, the staging of local disease can be further augmented by colonoscopic EUS guided fine needle aspiration of extra rectal lesions lying within or outside of the mesorectum that are demonstrated on cross-sectional imaging[23].

The need for highly accurate staging for early rectal cancer and early stage disease is highlighted by the observation that the National Bowel Cancer Screening Programme in the United Kingdom will result in an increase in the proportion of early stage tumours that are potentially amenable to local excision, although stage migration has yet to be demonstrated in population-based studies. Local recurrence rates of < 5% after TEM excision have been reported for pT1 tumours with favourable histology that equate to those achieved by radical surgery. As local excision offers the possibility of organ preservation and thus improved quality of life, recent focus has therefore shifted toward the use of neoadjuvant therapy as a means of downstaging early tumours (cT1-T3a) and sterilizing the mesorectal nodal field before local excision.

TREATMENT STRATEGY

Given the reluctance to administer neoadjuvant radiotherapy in early rectal cancer, there is a lack of data addressing the oncological outcomes and morbidity profile of this approach. This prompted us to undertake our systematic review of LE after neoadjuvant therapy to determine oncological outcomes as defined by LR and, second, to determine the incidence and nature of postoperative complications[20]. A total of 22 unique studies reporting on 1068 patients were analysed. Pre-treatment T2 and T3 tumours accounted for 46.4% and 30.7% of cases, respectively and LCCRT was administered in all studies, except to a cohort of 64 patients who received SCRT. The pooled cCR based on the staging modalities used in these studies was 45.8% with a pooled pCR 44.2%. At a median follow-up of 54 months, ypT0 tumours had a pooled local recurrence rate of 4% and a median disease-free survival rate of 95%. This compared favourably to results achieved with radical surgery in equivalent stage disease. Outcomes for ≥ ypT1 tumours were much worse with pooled local recurrence and disease-free survival of 22% and 68%, respectively[20]. Despite the obvious limitations of study heterogeneity and their retrospective nature, we conclude that local excision should only be considered as a definitive therapy if a pCR, i.e., ypT0, is obtained in the excision specimen.

The other unresolved issue is whether radiotherapy should be used in an adjuvant setting to improve outcomes after local excision of early rectal cancer, specifically in pT1 disease with unfavourable histology and pT2/pT3a disease. It is our current practice to offer local excision alone to patients with pT1 disease with favourable histology. Where post-operative histology reveals pT1 disease with adverse histological features or unexpected pT2 disease, we offer completion radical surgery as the standard of care and reserve adjuvant LCCRT for patients either deemed unfit or who wish to preserve their rectum. Even though much of the recent work in this field has focussed on the use of neoadjuvant therapy prior to local excision, we conducted our own systematic review of local excision followed by adjuvant therapy to determine if this was an acceptable treatment option. In this review, 22 studies described 804 patients who underwent local excision followed by adjuvant therapy either for unfavourable histology, prohibitive comorbidity or patient choice. T1, T2 and T3 tumours accounted for 35.1%, 58.0% and 6.9% of cases, respectively. Adjuvant regimens were exclusively long course in nature and included radiotherapy either alone or combination with chemotherapy. At a median follow-up of 51 months, the pooled local recurrence was 5.8% for pT1 tumours, 13.8% for pT2 tumours and 33.7% for pT3 tumours[24]. This suggests that it is possible to achieve reasonable local control in pT1 disease, even if adverse histological features are present, with post-operative adjuvant therapy. Clearly, this treatment strategy must be offered in the context of the significant body of evidence for radical surgery and the clinician most weigh up the balance of organ preservation, quality of life, patient choice and oncological outcome on an individual patient basis.

AUGMENTING THE RESPONSE TO RADIOTHERAPY

Tumour regression following neo-adjuvant chemo-radiotherapy is significantly associated with 5-year overall survival, disease-free survival and local recurrence[25,26], thus increasing our understanding of treatment adjuncts that might enhance tumour response to therapy. Also, adjuncts might increase the likelihood of pCR or near-pCR in patients with rectal cancer. A systematic literature search was conducted and all studies investigating the use of drugs to enhance response to neoadjuvant radiation in rectal cancer. However, the small number of studies and the heterogeneity of outcomes precluded systematic review and meta-analysis from being undertaken[27]. We therefore outlined the evidence to date in a narrative review and explored the potential mechanisms of action. Despite the obvious limitations, aspirin, metformin and statins appear to be associated with down staging rectal tumours and thus could potentially play the role of adjuncts in neoadjuvant therapy[28-31]. Moreover, provisional research strongly supports the potential role for the use of aspirin to induce apoptosis and enhance the effect of pre-operative radiotherapy[31]. This has prompted us to conduct a proof of principle prospective cohort study comparing patients who are taking aspirin to those who do not whilst receiving neo-adjuvant chemoradiotherapy prior to laparoscopic and open resection for rectal cancer (the ASPIRE study). The end points for this proof of principle study are both traditional surrogate markers of oncological outcome and laboratory markers of response to chemoradiotherapy.

FOLLOW UP IN PATIENTS WITH AN APPARENT COMPLETE CLINICAL RESPONSE

Around 15%-25% of tumours have a pCR[32,33], which is associated with a reduction in local recurrence and improved disease-free and overall survival[34,35]. Despite the difficulties in predicting pCR based on clinical and radiological findings, there appears to be increasing evidence that patients who exhibit an apparent cCR could be safely managed by local procedures, such as TEMS, TEO or TAMIS, to the tumour site or indeed intensive surveillance, the so called “watch and wait” strategy, to avoid the morbidity associated with radical surgery and enable organ preservation[36-38]. There is a paucity of evidence on the optimum follow up of such patients and we have therefore erred on the side of caution with intensive follow up for in the first 2 years that consists of endoscopic evaluation ± mucosal biopsy, MRI, EUS and CT every 3 months. The surveillance interval is then extended to 6 months, thereafter. Large prospective cohort studies will be required to educate this debate.

CONCLUSION

We provide treatment for early rectal cancer that is both patient-centred and based on the available evidence. This follows a detailed staging strategy that consists of clinical examination, CT, MRI, PET and the use of colonoscopic EUS with or without fine needle aspiration of extramural pelvic disease. All cases are discussed at a weekly multidisciplinary meeting where the patient’s comorbidities, quality of life and preferences are discussed in conjunction with the likely oncological outcomes of the potential treatment regimens on offer. Consent is usually a two or three-staged process where the patient’s treatment options are discussed in detail. Rather than adopting a protocol-driven strategy, we are strong advocates of using an evidence-based strategy that is tailored to the individual patient. In patients in whom we can confidently predict favourable T1 disease we would offer local excision, either by TEM or standard transanal excision as appropriate, or radical resection. In patients who opt for local excision and have pT1 disease with unfavourable histology, then we would offer adjuvant LCCRT in addition to standard radical resection. For pT2 disease and above, oncological options are compromised, and we would strongly recommend completion radical surgery. In patients with cT1/T2 disease that appears amenable to local excision, we offer the options of neoadjuvant therapy prior to LE or conventional resection. If patients elect to undergo neoadjuvant therapy and local excision, then we undertake a detailed assessment of treatment response using endoscopy, colonoscopic EUS and MRI prior to surgery. If a cCR is demonstrated, then we will operate a watchful waiting policy in selected cases. Where a significant partial response or near-cCR has been obtained, then we would proceed to local excision. This also gives us the option to offer completion radical surgery if there has been minimal tumour regression or the disease has progressed despite neoadjuvant treatment.

While the STAR-TREC trial aims to compare differing neoadjuvant regimens with radical surgery in early rectal cancer (T1-T3a)[38], a direct comparison of neoadjuvant and local excision versus local excision and adjuvant therapy has never been compared in a prospective study. It is possible that this debate may never been resolved with randomized controlled trials owing to the complexity in study design. It is likely that the neoadjuvant *vs*. adjuvant debate may only be answered with the use of large scale prospective registries. The management of early rectal cancer that combines local excision techniques with neoajuvant/adjuvant therapy is an evolving area of practice and we await the results of future studies with interest.

In patients with pT2 disease with unfavourable histology or pT3 disease not breaching the mesorectal resection margin (based on MRI) we offer conventional laparoscopic or open anterior resection with or without short course radiotherapy. In patients with more advanced disease our preference is to routinely offer pre-operative CRT followed by surgery in 3-6 months. Indeed, we are moving towards at least 3 months following CRT after post-operative re staging. In patients with low disease not suitable for anterior resection or local excision we favour extralevator abdominoperineal excision with immediate biologic mesh reconstruction of the pelvic inlet augmented by the use of myocutaneous flaps where indicated[39,40]. Our use of myocutaneous flaps has evolved over the last 10 years and we have recently found that bilateral gluteal advancement flaps provide excellent healing and quality of life (unpublished data, Thomas, Warr, Longman, Messenger).

DECLARATIONS

Authors' contributions

Clinical and scientific data: Thomas MG, Messenger DE, Gash K
Systematic review data: Thomas MG, Messenger DE
Manuscript preparation: Thomas MG, Messenger DE, Gash K

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Mini-invasive Surgery

Review

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Is robotic rectal resection the preferred option for resectable cancer?

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Abstract

The ultimate goal of rectal cancer surgery is to achieve a negative circumferential, distal resection margin and intact mesorectal excision; however, controversy remains as to what is the best approach. Based on the current evidence, open surgery remains the "gold standard", however recent improvements in minimally invasive surgery (MIS) techniques with the introduction of robotic surgery and transanal total mesorectal excision have questioned the historical approach of open rectal dissection. A robotic system (da Vinci) overcomes many of the limitations of laparoscopic surgery. A robotic system is more like an open surgery: it gives a 3-dimensional magnified view, endowrist movements, has a shorter learning curve when compared with laparoscopic surgery, with the added advantage of an MIS procedure. However, the higher cost associated with robotic surgery has limited uptake of this approach in rectal cancer surgery in many parts of world.

Keywords: Rectal cancer, open surgery, robotic surgery

INTRODUCTION

Complete mesorectal excision in the total mesorectal excision (TME) plane, as popularised by Prof. Heald, is the ultimate goal of rectal cancer surgery, as this technique has been shown to reduce local recurrence rates. The controversy, though, lies in defining the best approach to achieve good quality TME. Laparoscopic colorectal resection has been shown to improve postoperative pain, reduce blood loss, reduce the ileus rate, as well as lead to earlier recovery and hospital discharge[1]. However, data on oncological outcomes after laparoscopic rectal resection has shown no increase in overall or disease-free survival[2-4], and studies have suggested caution in the use of laparoscopic surgery in rectal cancer surgery as it is associated with higher circumferential resection margin (CRM) positive rates, when compared with open surgery[5]. Some inherent difficulties with laparoscopic surgery, such as working with rigid straight instruments in a narrow pelvis, 2-dimensional unmagnified views, and poor ergonomics, may have partly affected the oncological outcomes and increased the rates of positive CRM seen with laparoscopic surgery[5].

A robotic platform overcomes some of the limitations of laparoscopic surgery, delivering magnified 3-dimensional views, articulating instruments, offering a stable platform, an extra arm for retraction, and the ability for the surgeon to sit and operate. A meta-analysis comparing laparoscopic surgery with robotic surgery in rectal cancer surgery has shown robotic surgery to be safe, and shown better mesolectal dissection with robotic surgery[6,7]. Transanal TME (taTME) is a relatively new approach in rectal cancer resection and the oncological outcome of this approach is yet to be established in rectal cancer surgery. The aim of this review is to investigate the evidence and show that a robotic platform is the best minimally invasive surgery (MIS) approach for rectal cancer surgery.

WHY ROBOTIC SURGERY FOR RECTAL CANCER

Technical advantages of robotic surgery

A robotic platform, in comparison with laparoscopic surgery, is more ergonomic, reduces tremors, provides magnified 3-dimensional views, provides an extra working arm and gives the surgeon control of stable camera movements[8]. All these advantages surely help surgeons perform a very precise dissection of the TME plane, preserving the autonomic nerves[9]. However, due to the loss of haptic feedback with a robotic system, it is relatively easy to cause tissue damage during dissection and traction if not careful. A console surgeon can overcome the tactile feedback limitations of a robotic system by using visual cues, coupled with experience[10].

Questionable safety of laparoscopic rectal dissection

Laparoscopic surgery has been shown to have improved short-term outcomes including less postoperative pain, reduced ileus rate, early discharge and return to work, however the safety of laparoscopic surgery in rectal cancer surgery is questioned. In a classic trial, laparoscopic surgery was associated with increased CRM positivity rates compared with open surgery (12.4% *vs.* 6.3%). Laparoscopic rectal cancer surgery in particular is associated with a higher conversion rate when compared with colonic laparoscopic resection, and those that are converted to open surgery have a higher mortality rate[5,11]. This is a possible reflection of the technical challenges that confront a surgeon during rectal dissection. Recent multicentre randomized controlled trials (RCTs) have shown that the laparoscopic approach may have a higher potential for inferior quality TME[12], however the long-term data on oncological outcomes are still awaited from these trials.

Potentially better oncological outcomes with robotic rectal surgery

A multicentre study reported excellent short term oncological outcomes with robotic rectal surgery (97% 3-year overall survival)[13]. Non-randomised data out of Korea have shown similar results[14]. The three-year overall survival is 93.1%, with disease-free survival of 79.2%, a low CRM positivity rate of 5.7% and a local recurrence rate of 3.6%: results which are equivalent to laparoscopic surgery from the same group[15]. Although long term data on oncological outcomes with robotic rectal surgery are still lacking, better oncological outcomes and the low CRM positivity rates seen with robotic rectal surgery are a possible reflection of better visualisation, and the better ergonomic, stable platform that comes with robotic technology[16,17].

Kim *et al.*[18] recently reported a trend towards improved overall survival and cancer-specific survival rates with a robotic resection for mid to low rectal cancer (meaning the tumour height from the anal verge was 6.8 cm), compared with a laparoscopic resection in a retrospective, propensity score matched analysis (224 patients

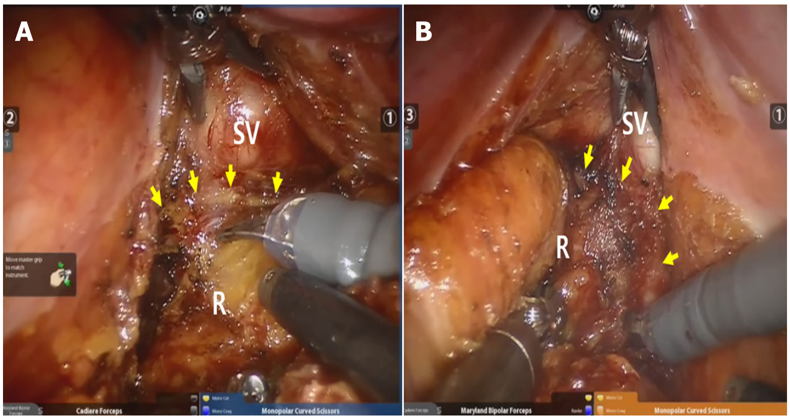

Figure 1. (A) The left neurovascular bundle (arrows) attached to the left seminal vesicle (SV) is dissected from the rectum (R); (B) the right neurovascular bundle (arrows) attached to the right SV is dissected from the R

each). In multivariate analyses, the robotic approach was a significant positive prognostic factor for overall survival and cancer-specific survival (P = 0.0040, HR = 0.333; P = 0.0161, HR = 0.367).

Lower conversion rates with robotic rectal surgery

As shown in a classic trial, higher conversion rates are associated with poor oncological outcomes and higher mortality. A meta-analysis comparing robotic surgery with laparoscopic surgery found robotic surgery to be associated with a lower conversion rate than open surgery[19], a finding seen in two other studies[20,21]. This potentially may allow the surgeon to complete many challenging rectal cancer cases using MIS with similar oncological outcomes. Data from the robotic *vs.* laparoscopic resection for rectal cancer (ROLARR) trial have shown that robotic surgery reduced the conversion rate in obese males with low rectal cancer, a challenging group for laparoscopic surgery[22].

Shorter learning curve with robotic surgery

The learning curve for laparoscopic colorectal surgery ranges between 30-70 cases[23]. A robotic platform which emulated open surgery with the advantage of a 3-dimensional magnified view, using articulating instruments (as compared with the straight instrument in laparoscopy) and better ergonomics has been shown to have a shorter learning curve, at some 20 cases[24,25]. However, the loss of haptic feedback with robotic surgery may confound the robotic learning curve. An initial learning period of 30-40 cases and experience in visual cues lead to the second phase, where surgeons start taking on more complex cases.

Better chance for nerve preservation

Studies comparing sexual dysfunction between laparoscopic surgery and open surgery have shown that sexual function is significantly impaired after laparoscopic surgery[26-28]. However, robotic surgery has shown improved post-operative sexual dysfunction and earlier functional recovery, compared with laparoscopic surgery[29]. Improved sexual and urinary functions after robotic surgery are reflections of better nerve visualisations using a 3-dimensional magnified robotic platform [Figure 1].

Ability to assess vascularity of anastomosis

It is well known that distal perfusion is one of the main technical factors that affect the leak rate[30]. Measures such as bleeding from marginal vessels, mesenteric vessel pulsation, a lack of distal end discolouration and negative leak tests are all unreliable and do not help predict postoperative leaks[31]. Indocyanine green (ICG) which is absorbed near infrared light[32] and detected by a robotic NIR camera system helps assess the distal bowel vascular supply and decrease anastomotic leak[33]. In one study, the use of ICG has shown a 60% reduction in the leak rate[34]. It also visualizes unusual vascular anatomy such as the Arc of Riolan[35]. Use of

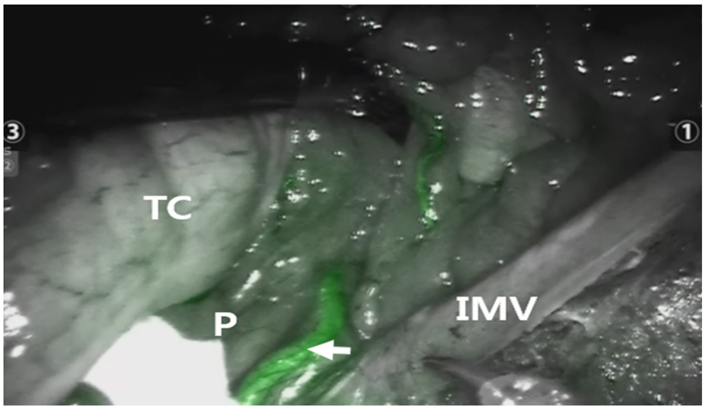

Figure 2. The Arc of Riolan (arrow) is highlighted by indocyanine green fluorescence during a high ligation of the inferior mesenteric vein (IMV) close to the pancreas (P). The transverse colon (TC) is cephalad retracted

Figure 3. The rectum is transected with guidance of indocyanine green fluorescence to confirm good perfusion on the distal rectal stump

ICG is also gaining popularity in identifying bilateral ureters and positive lateral pelvic lymph nodes during robotic rectal surgery [Figures 2 and 3].

The Arc of Riolan can be highlighted by indocyanine green fluorescence during a high ligation of the inferior mesenteric vein close to the pancreas. The transverse colon is cephalad retracted. When the Arc of Riolan exists, it should be preserved for better perfusion to the proximal segment of the anastomosis after rectal resection[35] [Figures 2 and 3].

Ability to perform an advanced MIS procedure robotically

The optimal surgical approach for a positive lateral pelvic node has yet to be established in rectal surgery. Lateral node dissection is associated with increased blood loss and risk of damage to pelvic nerves, however the safety and feasibility of the robotic approach in pelvic lateral node dissection has been demonstrated[36,37]. The ability to perform precise dissection with the stable robotic platform and the use of ICG to identify positive lateral nodes may potentially reduce the morbidity associated with this procedure.

Studies have shown that precise dissection of the lower rectum, in particular intersphincteric dissection, is associated with better long term functional and oncological outcomes[38,39]. The robotic platform allows for a very precise dissection of the lower third of the rectum in the very confined space of the deep pelvis. Precise robotic intersphincteric dissection also potentially reduces the duration of the perineal procedure[40,41].

Transanal TME *vs*. robotic TME

Despite advances in surgical management of rectal cancer, and advances in different minimally invasive approaches, achieving negative CRM remains a challenge, particularly in rectal tumours in the lower 1/3[42]. To overcome this, and to avoid higher costs associated with robotic procedures, taTME has emerged as a new technique for performing rectal dissection[43,44]. Proponents of taTME believe that this is the best approach for rectal dissection, as this technique offers great access to distal 1/3 rectal dissection, a good view of the pelvic anatomy, the ability to define the distal resection margin and potential for double purse-string anastomosis. A multicentre study comparing robotic TME to taTME has found that high quality TME can be achieved by both robotic and transanal approaches in skilled hands[45]. However, long term data on oncological and functional outcomes of taTME are yet to be established.

CONCLUSION

Robotic rectal cancer surgery is safe and feasible and overcomes some of the shortcomings of laparoscopic surgery. This may be the reason why robotic surgery has better oncological and functional rates, along with lower conversion rates when compared with laparoscopic surgery. However, robotic surgery is yet to be compared with open surgery, "the gold standard of rectal cancer resection". The higher costs associated with robotic surgery have been the major drawback in uptake of robotic surgery worldwide[46]. However, new robotic platforms coming out in the future may reduce the cost of robotic surgery. Surgery technology continues to advance in order to overcome the limitation of current surgical practice. Innovation is rapid, but adoption of new technology occurs over time. Further prospective clinical trials will verify the true role of the robot in rectal surgery.

DECLARATIONS

Authors' contributions

All authors made substantial contributions to: conception, design, acquisition and drafting the article and revising it critically for important intellectual content; and gave final approval of the version to be published.

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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Mini-invasive Surgery

Review

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Minimal invasive approach for beyond total mesorectal excision/extended resections in rectal cancer

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Abstract
Minimal invasive surgery (MIS) is an accepted modality of treatment for rectal cancer. The indications for MIS have gradually been extended to locally advanced and locally recurrent rectal cancer as a result of technological advances in instrumentation, advances in surgical techniques, increased surgeon experience, and high volume center. However, safety and feasibility of laparoscopic surgery and robotic surgery in beyond total mesorectal excision (b-TME) and extended TME (e-TME) are not well established. This review summarizes the current evidence for MIS approach for b-TME/extended resections in rectal cancer. A systematic search was carried out in PubMed. Studies available in English related to MIS approach in b-TME/e-TME in rectal cancers were identified and evaluated. This review concludes MIS is feasible with good perioperative outcomes in b-TME/e-TME in carefully selected patients. Laparoscopic surgery has considerable learning curve and should be performed by experienced surgical teams. Robotic surgery is feasible and beneficial in complex resection in pelvis. However, evidence for long-term oncological outcomes of MIS in b-TME/e-TME is low and needs to be studied further by randomized controlled trial once enough numbers are possible in institutes with high volume rate.

Keywords: Minimal invasive surgery, laparoscopic surgery, robotic surgery, beyond total mesorectal excision, extended resection, locally advanced rectal cancer, pelvic exenteration, lateral pelvic lymph node dissection

INTRODUCTION
Total mesorectal excision (TME) is a standard of care for primary rectal cancer located within mesorectal fascia. In locally advanced and locally recurrent tumors extending beyond mesorectal fascia, removal of

total mesorectum along with *en bloc* resection of involved pelvic structures often required to achieve R0 status[1]. Magnetic resonance imaging (MRI) of pelvis is accurate in staging of locally advanced and locally recurrent rectal cancer[2,3]. On the basis of the involvement of fascial boundaries and the anatomic planes of dissection between intra-pelvic organs in the MRI, pelvis was divided into seven compartments, namely the central, peritoneal reflection, anterior above and below the peritoneal reflection, posterior, lateral, and inferior compartments[4]. The locally advanced and locally recurrent rectal cancers were classified depending on the MRI findings of tumor invasion within seven intra-pelvic compartments[2].

The extended-TME (e-TME) is defined as partial resection of adjacent organ(s) of the rectum such as posterior wall of the prostate or the vagina, the uterus, the seminal vesicles, the hypogastric plexuses, the ureter, and bladder *en bloc* with the TME with curative intent, to achieve a R0 resection[5,6]. The beyond-TME (b-TME) includes posterior pelvic exenteration, total pelvic exenteration, extralevator abdomino-perineal resection for inferior compartment involvement, and sacral resection for posterior compartment involvement[5,7]. Lateral pelvic lymph node dissection is considered for subgroup of patients with clinically suspected lateral pelvic lymph node metastasis, even after neo-adjuvant chemo-radiotherapy[8,9].

Only few specialized multidisciplinary units across the world perform these aggressive resections as the morbidity and mortality associated with these surgeries is very high[10]. Refinement and standardization of these techniques forge the way forward in improving outcomes. Multidisciplinary team approach, advances in surgical technique, perioperative care, interventional radiology, and better patient selection have contributed to the decrease in complication rates, making it feasible for an increasing number of surgical units to adopt these aggressive surgical techniques.

Minimal invasive surgery (MIS) is an accepted modality of treatment for rectal cancer. Laparoscopic resection improves perioperative outcomes, including decrease in intraoperative blood loss, postoperative pain, ileus, and duration of hospital stay. Randomized trials such as the CLASICC (Conventional *vs.* Laparoscopic-Assisted Surgery in Colorectal) trial, COREAN (Comparison of Open *vs.* Laparoscopic Surgery for Mid or Low Rectal Cancer after Neoadjuvant Chemoradiotherapy) trial, and COLOR II (Colorectal Cancer Laparoscopic or Open Resection II) trials have confirmed the feasibility and oncological safety of laparoscopic surgery in TME[11-13]. Despite the advantages, laparoscopic surgery has some limitations, such as unstable, two-dimensional view, limitations in the freedom degrees of the surgical instruments, the amplification of the physiological tremor and the "fulcrum" effect, and poor ergonomics[14,15]. The robotic surgery overcomes these disadvantages and improves the ergonomics of the surgeon[16]. The robotic surgery helps reduce hospital stay and conversion rates and similar oncological outcomes in TME[17-19]. But recently, ROLARR (RObotic *vs.* LAparoscopic Resection for Rectal Cancer) trial revealed that robotic-assisted laparoscopic surgery do not confer an advantage over laparoscopic surgery in rectal cancer resection for TME[20]. However this trial did not address the e-TME/b-TME.

The aforementioned randomized trials have excluded cT4 lesions. Bretagnol *et al.*[21] assessed feasibility and oncological outcomes of laparoscopic surgery for cT4 colorectal cancer and suggested that locally advanced rectal cancer cannot be considered as absolute contraindication. A multicenter propensity score-matched analysis of laparoscopic surgery *vs.* open surgery for T4 rectal cancer by de'Angelis *et al.*[22] suggested that laparoscopic surgery can achieve good pathological and oncological outcomes similar to open surgery with faster recovery and shorter hospital stay, despite the risk of conversion. The indications for MIS have gradually been extended to locally advanced and locally recurrent rectal cancer as a result of technological advances in instrumentation, advances in surgical techniques, increased surgeon experience, and high volume center, which suggested laparoscopic surgery is feasible with good perioperative outcomes[23-25]. Kim *et al.*[26] reported that laparoscopic multivisceral resection seems to be a feasible and effective treatment option for colorectal cancer for carefully selected patients without any adverse long-term oncological outcomes. However, safety and feasibility of laparoscopic and robotic surgery in b-TME and e-TME are not well established, and there are very few studies in the world literature. This review summarizes current evidence for MIS approach for b-TME/extended resections in rectal cancer.

METHODS

A systematic search was carried out in PubMed. Studies available in English related to MIS approach in b-TME/e-TME in rectal cancers were identified and evaluated. Keywords used were "MIS, laparoscopic surgery, robotic surgery, b-TME, e-TME, locally advanced rectal cancer, pelvic exenteration, extended resection, lateral pelvic lymph node dissection, abdominosacral resection". The perioperative outcomes such as duration of surgery, blood loss, conversion rate, overall morbidity, hospital stay, R0 status, and long-term outcomes such as local recurrence rate, disease-free survival, and overall survival (OS) were studied.

PELVIC EXENTERATION

Local control and long-term survival in locally advanced and locally recurrent rectal cancer mainly depend on R0 resection[1]. Complete *en bloc* resection of the tumor along with adjacent structures depending on the location and depth of invasion is important to achieve R0 status[27]. Pelvic exenteration by open approach is a standard of care for locally advanced and locally recurrent rectal cancer. MIS for pelvic exenteration is not well established. Only few studies have been described and have confirmed the feasibility and short-term outcomes. Whenever feasible and appropriate, MIS can be performed.

The locally advanced and locally recurrent rectal cancers with invasion limited to the anterior pelvic organ are good candidates for laparoscopic pelvic exenteration as a free circumferential margin can be achieved easily[28]. The b-TME Collaborative has generated a consensus guideline suggesting certain contraindications for these resections[7], which holds true for MIS also. Absolute contraindications are poor performance status/medically unfit patients, bilateral sciatic nerve involvement, and circumferential bone involvement. Relative contraindications include extension of tumor through the sciatic notch, encasement of external iliac vessels - requiring *en bloc* resection and/or reconstruction of external iliac vessels, high sacral involvement (above S2/S3), and predicted R2 resection. Patients who underwent multiple laparotomies and predicted to have severe small bowel adhesion are precluded from having MIS[29].

Initial experience in laparoscopic pelvic exenteration was reported in few case reports and video vignette[28,30]. Akiyoshi *et al*.[31] demonstrated an laparoscopic pelvic exenteration for locally recurrent rectal cancer and suggested that laparoscopic pelvic exenteration was a technically challenging procedure that requires a long operative time with benefits of a very clear view of the operative field, allowing precise dissection, less blood loss, and a smaller abdominal wound.

One of the initial experiences of laparoscopic pelvic exenteration come from Uehara *et al*.[29]. They discussed the technical points of laparoscopic pelvic exenteration and compared the short-term results of laparoscopic pelvic exenteration with those of conventional open pelvic exenteration. The surgeon performed posterior and lateral pelvic wall dissection in the initial part of surgery and anterior dissection in the last phase to avoid suspension of urinary bladder. Dissection along internal iliac vessels and identification and transection of small branches are important to avoid intraoperative bleeding[29]. The dorsal vein complex was clipped and divided using bipolar soft-coagulation of a VIO system. Investigators observed that laparoscopic-guided perineal approach avoided much blood loss by helping proper dissection. Intraoperative blood loss was significantly lower in laparoscopic pelvic exenteration group (830 *vs*. 2769 mL, $P = 0.003$), and operative time and rate of R0 resection were similar in both groups. The authors concluded that laparoscopic pelvic exenteration performed by an experienced pelvic surgeon was safe and efficient in carefully selected patients.

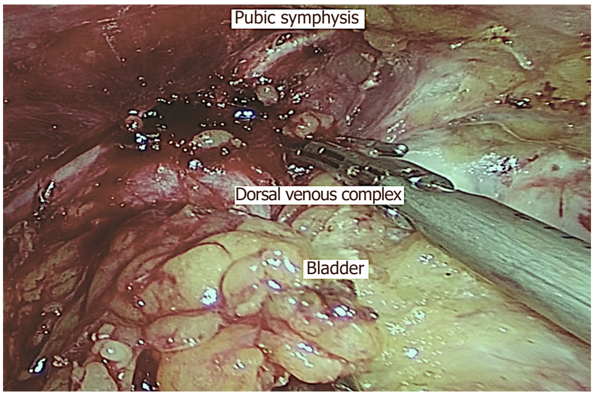

Figure 1. Laparoscopic pelvic exenteration with division of dorsal vein complex using Ligaclip and Harmonic Ace (Ethicon, India)

Ogura *et al.*[32] compared perioperative outcomes of laparoscopic pelvic exenteration (n = 13) with open approach (n = 18), and results were similar to those of Uehara *et al.*[29]. The estimated blood loss (930 *vs.* 3003 mL; P = 0.001) and total volume of blood transfusion (0 *vs.* 1990 mL; P = 0.002) were significantly lower in patients undergoing laparoscopic pelvic exenteration compared with those undergoing open pelvic exenteration. The operative time, complications rate, and postoperative hospital stay were similar in both the groups. According to the authors reduced blood loss in laparoscopic pelvic exenteration group was due to the high-definition, illuminated, and magnified view to detect smaller vessels and control the bleeding, and the high pneumoperitoneal pressure to reduce venous oozing. The dorsal vein complex was transected after intracorporeal suturing in most of the patients and when patient required sacral resection or perineal reconstruction, dorsal vein complex was divided under direct vision. There was no conversion to open and all achieved R0 resection. Investigator emphasizes on careful selection of patients, as those with tumors spreading only to the prostate and requiring total pelvic exenteration are better candidates than those with urinary bladder also being invaded and requiring anterior pelvic exenteration.

Our institute is a high volume referral center for colorectal cancer[33] and we do perform e-TME, b-TME, and multivisceral resection for locally advanced and locally recurrent rectal cancer[34-36]. We standardized our technique of laparoscopic pelvic exenteration[37,38]. We use standard five-port technique followed by medial-to-lateral retroperitoneal dissection, inferior mesenteric artery division, dissection of retrorectal space up to origin of levator ani, pararectal space dissection after medializing ureters, dissection of paravesical space to the level of the endopelvic fascia, dissection of Retzius space, division of dorsal vein complex, urethral transection, division of ureters, sigmoid transection, perineal dissection, and Bricker's ileal conduit through small infraumbilical incision. In patients who already have transverse stoma, previous stoma was retained and ureterosigmoid anastomosis was performed after stapling the sigmoid colon distal to the transverse stoma. We emphasize on transection of ureters at the end of abdominal part surgery for monitoring urine output and avoiding urine leak. We divide dorsal vein complex at the last stage of pelvic dissection using Ligaclip and Harmonic Ace (Ethicon, India) [Figure 1]. In case of bleeding, we would increase abdominal gas pressure, pack with tape gauze, and suture during perineal part of surgery. In our study, blood loss was 1000 mL (range 300-2000 mL), mean duration of surgery was 9.13 h (range 7-13 h), and mean postoperative stay was 14.6 days (range 9-25 days)[38]. When compared to other studies, we have demonstrated good perioperative outcomes [Table 1].

Hayashi *et al.*[39] reported that laparoscopic pelvic exenteration using transanal minimal invasive surgery has certain advantages. They claimed that good visual field in the pelvis can be maintained even after entry into abdominal cavity as pneumoperirectum is sustained by the pneumoperitoneum. The small perineal wound and less bleeding reduce the perineal surgical site infection. Uematsu *et al.*[40] also confirmed the advantages

Table 1. Case series of laparoscopic pelvic exenteration and outcomes

Study	Year	Number of patients (*n*)	Median operative time, min (range)	Median blood loss, mL (range)	Conversion to open (%)	Overall complications (%)	Hospital stay (days)	R0 status (%)	Follow-up (months)
Uehara *et al*.[29]	2015	6/48 (LPE/OPE)	935 (716-1219)	830 (283-5225)	16.7	66.7	27 (23-53)	77.8	NR
Ogura *et al*.[32]	2016	13/18 (LPE/OPE)	829	930	0	61.5	29	100	NR
Pokharkar *et al*.[38]	2018	10 (LPE)	547	1000 (300-2000)	0	20	14.6 (9-25)	100	NR

LPE: laparoscopic pelvic exenteration; OPE: open pelvic exenteration; NR: not reported

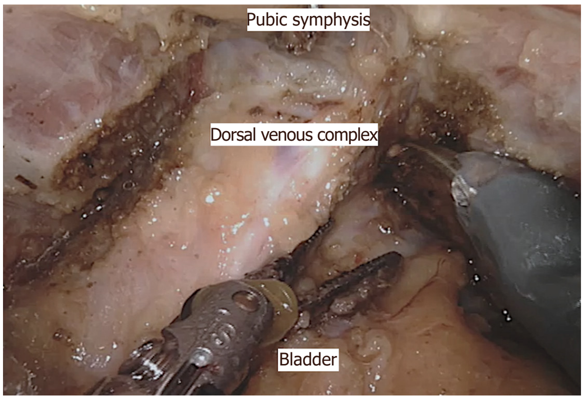

Figure 2. Robotic pelvic exenteration with division of dorsal vein complex

of transanal minimal invasive surgery during perineal part of laparoscopic pelvic exenteration. Investigator suggested that the division of dorsal vein complex is feasible and safe because of broader working area. Injury and bleeding from visceral pelvic fascia can be prevented by dividing the urethra at the junction with prostate and dissecting levator ani along the attachment of internal obturator muscle.

There are a few case series and reports on robotic pelvic exenteration for gynecological, urological, and locally advanced rectal cancer[41-43]. One of the first reports of robotic pelvic exenteration for locally advanced rectal cancer come from Shin *et al*.[44]. They described three cases including two extended resections with *en bloc* prostatectomy and intracorporeal vesicourethral anastomosis, and one total pelvic exenteration with intracorporeal ileal conduit. Winters *et al*.[45] compared robotic pelvic exenteration with laparoscopic rectus flap and open pelvic exenteration, and reported similar operative times with reduced blood loss, less narcotic usage, shorter intensive care unit stays, and shorter hospital stays. The surgical steps of robotic pelvic exenteration are similar to those of laparoscopic pelvic exenteration[46] [Figures 2, 3 and 4]. Long-term oncological outcomes need to be studied further to implement robotic pelvic exenteration as a standard procedure.

LATERAL PELVIC LYMPH NODE DISSECTION

The incidence of lateral pelvic lymph node metastasis in locally advanced mid- and low-rectal cancer ranges from 10% to 25%[47,48]. In Japan, lateral pelvic lymph node involvement is considered as loco-regional disease, and in West, it is regarded as systemic disease[49-51]. Thus, present strategies for the management of lateral pelvic lymph node are TME with neo-adjuvant chemo-radiotherapy and/or lateral pelvic lymph node dissection[47,52-54]. The recent study suggested that patients with lateral pelvic lymph nodes responsive to neo-adjuvant chemo-radiotherapy may not benefit from lateral pelvic lymph node dissection and subgroup with persistent lateral pelvic lymph node following neo-adjuvant chemo-radiotherapy may benefit from lateral pelvic lymph node dissection[8]. In our institute, we perform lateral pelvic lymph node dissection in selective

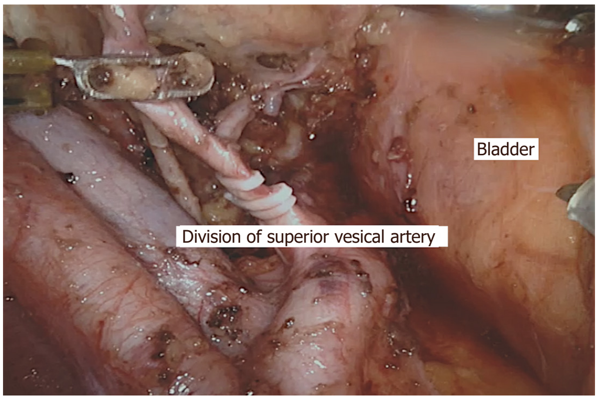

Figure 3. Robotic pelvic exenteration with lateral pelvic lymph node dissection showing division of vesicle artery

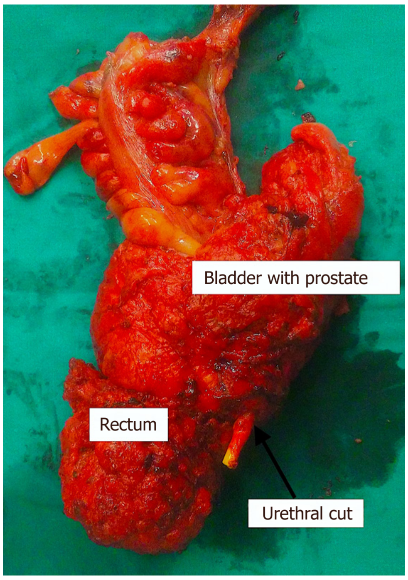

Figure 4. Specimen of total pelvic exenteration

patients with persistent lateral pelvic lymph node dissection after neo-adjuvant chemo-radiotherapy[34,35,55,56]. The template of lateral pelvic lymph node dissection in rectal cancer differs from that of genitourinary tract malignancy as it extends inferior to the plane of the obturator nerve up to pelvic floor[57] [Figure 5].

In extending the scope of MIS and its advantages over open approach, high volume centers initiated laparoscopic/robotic lateral pelvic lymph node dissection. One of the initial experiences by Liang[58] suggested that laparoscopic pelvic lymph node dissection is a technically demanding procedure and should be performed by highly experienced laparoscopic surgeons on carefully selected patients. Park *et al.*[59] reported the technical feasibility, safety, and oncological outcomes of laparoscopic lateral pelvic lymph node dissection following TME with mean number of lateral lymph nodes harvested to be 9.1 (range 3-19). Liu *et al.*[60] suggested that the laparoscopic radical correction combined with extensive lymphadenectomy and pelvic autonomic nerve preservation is feasible and safe.

Akiyoshi[61] reviewed the published series involving at least 10 patients with locally advanced low rectal cancer who underwent laparoscopic/robotic lateral pelvic lymph node dissection from 2011 to 2015 and opined that MIS is technically safe and feasible procedure with good perioperative outcomes when performed by

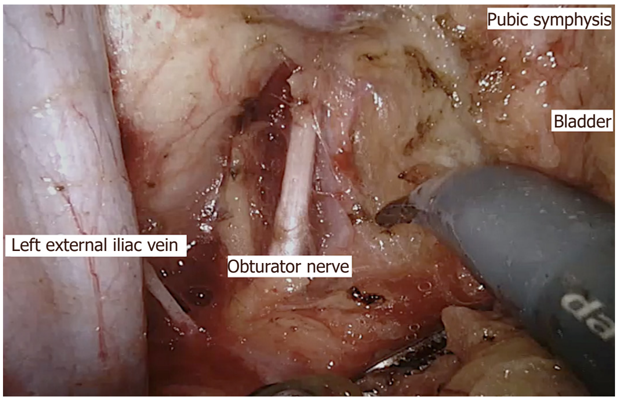

Figure 5. Robotic lateral pelvic lymph node dissection with dissection inferior to obturator nerve

experienced laparoscopic surgeons specializing in pelvic surgery. The author emphasized that lateral pelvic lymph node metastasis more commonly occurs around the distal internal iliac vessels located very deep in the pelvic space[49]. With magnified and illuminated vision of MIS and surgeons with good knowledge of lateral pelvic anatomy and sufficient experience in MIS TME procedure, lateral pelvic lymph node dissection can be performed meticulously with less blood loss[61].

Nagayoshi *et al.*[62] evaluated the feasibility and oncological safety of laparoscopic lateral pelvic lymph node dissection compared with the conventional open approach. The mean operative time was longer in the laparoscopic group than in the open group (641.0 *vs.* 312.0 min, $P < 0.001$). The laparoscopic group had less blood loss (252.0 *vs.* 815.0 mL, $P < 0.001$) and a shorter hospital stay (22.9 *vs.* 29.1 days, $P = 0.04$) than the open group. The morbidity rate and OS (3-year OS: 94.7% *vs.* 82.9%, $P = 0.25$) did not differ between the two groups. The mean number of harvested lateral pelvic lymph nodes was more in the laparoscopic group than in the open group (19.5 *vs.* 15.8, $P < 0.05$). In lateral pelvic lymph node dissection following neo-adjuvant chemo-radiotherapy, lymph node yield would be low[63] and studies have shown that the number of lymph nodes does not affect the recurrence rate and survival[64]. Furuhata *et al.*[65] confirmed the good oncological outcomes with perioperative morbidity of 16.7% as three patients developed grade 2 urinary retention.

Robotic surgery may facilitate lateral pelvic lymph node dissection because of its advantage over laparoscopic surgery. Initial small series have confirmed the feasibility of robotic lateral pelvic lymph node dissection[66,67]. In our institute, we standardized the technique of robotic lateral pelvic lymph node dissection[57]. We use standard five-port technique followed by completion of TME, medialization of ureter, skeletonization and dissection around external and internal iliac vessels, dissection of obliterated umbilical artery, dissection in paravesical space, standard template dissection, identification of obturator nerve, and dissection up to pelvic floor [Figure 6].

Kagawa *et al.*[68] reported short-term outcomes in 50 consecutive robotic lateral pelvic lymph node dissections. The median operative time was 165 min (range 85-257 min) and median blood loss was 27 mL (range 5-690 mL). The median number of harvested lymph nodes was 19 (range 5-47). There was no conversion to open or laparoscopic approach. Clavien-Dindo classification grade III-IV complications occurred in only one patient (2.0%).

Yamaguchi *et al.*[69] compared short-term outcomes of robotic-assisted laparoscopic lateral pelvic lymph node dissection with open approach. Operative time was significantly longer in the robotic surgery ($P = 0.007$). The blood loss and perioperative complications were significantly less in the robotic group.

Kim *et al.*[70] have compared robotic lateral pelvic lymph node dissection with laparoscopic approach. There was no significant difference in operative time between the two groups (robotic *vs.* laparoscopic, 41.0 ± 15.8 min *vs.*

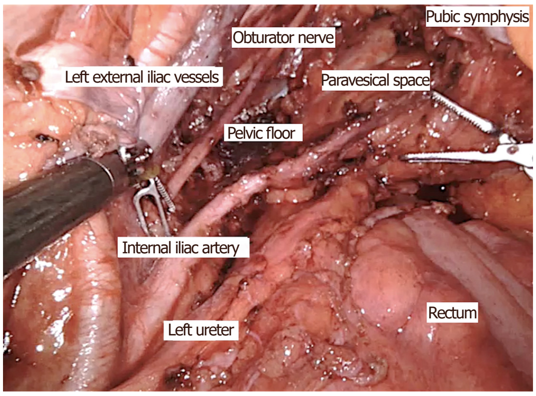

Figure 6. Robotic surgery showing template of lateral pelvic lymph node dissection

35.3 ± 13.4 min; *P* = 0.146), but the estimated blood loss was significantly lower in the robotic group (34.6 ± 21.9 mL *vs*. 50.6 ± 23.8 mL; *P* = 0.002). Seven patients in the laparoscopic group and two in the robotic group developed urinary retention postoperatively (*P* = 0.029). The mean number of harvested lateral pelvic lymph nodes was 6.6 (range 0-25) in the robotic group and 6.4 (range 1-14) in the laparoscopic group. Three patients (6.0%) in the robotic group and four (11.4%) in the laparoscopic group developed local recurrence (*P* = 0.653).

Thus, short-term outcomes of MIS for lateral pelvic lymph node dissection are acceptable and long-term oncological outcomes need to be studied further [Table 2].

EXTENDED RESECTION

Locally advanced rectal cancer adherent to adjacent organs in 10%-20%, might be due to direct invasion or inflammation[68]. In locally recurrent rectal cancer, the plane of dissection would be very difficult due to severe fibrosis from previous surgery and adhesions between neo-rectum and adjacent organs[24]. *En bloc* resection of tumor along with adjacent organs is required to achieve negative margin and to prevent exposure and dissemination of tumor cells as it is difficult to determine if these adhesions are benign or malignant[23,33]. Several studies suggested that *en bloc* resection of prostate/seminal vesicle is an acceptable option to avoid total pelvic exenteration in selected patients[23,71,72]. The controversy still exists on options of treatment following neo-adjuvant chemo-radiotherapy in locally advanced rectal cancer with adjacent organ involvement. A recent study by Denost *et al*.[5] suggested that TME or e-TME are technically and oncologically feasible and should be considered in preference to b-TME in responders. They also reported that b-TME procedures should be preferred in non-responders, allowing for high rates of morbidity and local recurrence in patients with e-TME.

In our institute, extended resections are performed in carefully selected patients by balancing oncological safety and complications such as impaired urinary and sexual functions, as most of the patients belong to younger age group[33]. However, achieving an R0 resection is the primary goal of surgery. We do perform these resections by MIS approach[35]. Seminal vesicle is the most common adjacent organ involved in male patients[73]. We standardized our technique of laparoscopic seminal vesicle excision along with TME in locally advanced rectal cancer[35]. Technique differs from standard TME in anterior plane of dissection. Anterior peritoneal dissection started higher on urinary bladder followed by identification and division of vas deferens, dissection of distal ureter, identification of seminal vesicle, and dissection anterior to seminal vesicle till Denonvilliers' fascia is cut [Figures 7 and 8]. The most important step of surgery is identification and dissection of ureter where it arches below the vas deferens mostly when the disease involves tip of seminal vesicle [Figure 9]. If the base of seminal vesicle is involved, the ureters are usually spared.

Table 2. Case series of laparoscopic/robotic lateral pelvic lymph node dissection and outcomes

Study	Year	Number of patients (*n*)	NACT/RT (%)	Median operative time, min (range)	Median blood loss, mL (range)	Conversion to open (%)	Overall morbidity (%)	Hospital stay (days)	Median LN yield (*n*)	Median positive LN, *n* (%)	Median follow-up (months)	Recurrence (%)	OS (%)
Liang[58]	2011	34 (LL)	100	58 (42-94) for UL	44 (20-240) for UL	0	20.6	9 (7-35)	6 (2-14)	2.2 (71)	24	27.3 (OR), 5.8 (LR)	NR
Park *et al*.[59]	2011	16 (14 LL, 2 RL)	56	310 (220-510)	188 (50-370)	0	31.2	9.9 (7-14)	9.1 (3-19)	9 (56.2)	38 (6-81)	11.2(LR)	NR
Liu *et al*.[60]	2011	68 (LL)	NR	271	150	NR	7.4	11	23	7	NR	NR	NR
Nagayoshi *et al*.[62]	2016	46 (LL)	52.2	641 (356-984)	252 (25-1267)	0	43.47	22.9 (9-64)	19.5 (3-43)	7 (15.2)	NR	26.3 (OR)	94.7 (3 years)
Furuhata *et al*.[65]	2015	18 (LL)	0	603.7 (473-746)	380 (10-930)	0	16.7	25.5 (9-56)	17 (7-27)	28	23.6 (11.9-41.4)	5.5 (OR)	NR
Park *et al*.[66]	2012	8 (RL)	100	38 (20-51) for UL	48 (20-100)	0	25	7.5 (5-12)	4.1 (1-13)	3(38)	NR	NR	NR
Bae *et al*.[67]	2014	21 (11 RL, 10 LL)	86	396 (170-581)	200 (50-700)	0	29	10 (5-24)	7 (2-23)	0	14	14.3	NR
Kagawa *et al*.[68]	2015	50 (RL)	12	476 (320-68)	27 (5-690)	0	14	8 (6-13)	19 (5-47)	20	NR	NR	NR
Yamaguchi *et al*.[69]	2016	85 (RL)	11.8	455 (249-683)	25 (0-690)	0	30.6	8 (6-15)	19 (5-62)	16.5	NR	NR	NR
Kim *et al*.[70]	2018	85 (50 RL, 35 LL)	NR	41.0/35.3 for UL	34.6/50.6 for UL	0	4/20	NA	6.6 (0-25)/ 6.4 (1-14)	28.0/41.2	26.3	30/31.2 (OR), 6.0/11.4 (LR)	NR

NACT/RT: neo-adjuvant chemotherapy/radiotherapy; LN: lymph node; OR: overall recurrence; LR: local recurrence; OS: overall survival; LL: laparoscopic lateral pelvic lymph node dissection; RL: robotic lateral pelvic lymph node dissection; UL: unilateral; NA: not available; NR: not reported

One of the initial reports on laparoscopic multi visceral resection comes from Bretagnol *et al*.[21]. In this study, there were 12 locally advanced rectal cancers with adjacent organ involvement. The authors opined that laparoscopic surgery is feasible with good perioperative outcomes. Kim *et al*.[26] reported their experience in laparoscopic multi visceral resection, including six partial cystectomies, seven seminal vesicle excisions, and three prostatectomies with seminal vesicle resection. Two patients developed urinary fistula following prostatectomy. The authors emphasized that experienced urologist can reduce the urinary complications. There was no difference in R0 resection rate, local recurrence rate, or OS between the laparoscopic and open surgery group. The authors confirmed that laparoscopic extended resections in locally advanced rectal cancer are oncologically safe with good perioperative outcomes in carefully selected patients.

Nagasue *et al*.[24] compared perioperative outcomes of laparoscopic *vs.* open multi visceral resection. There were six partial cystectomies, four seminal vesicle excisions, one prostatectomy, seven partial vaginal wall excisions, and six levator ani muscle excisions in the laparoscopic group. The authors claimed that *en bloc* resection of the vagina or pelvic floor muscle could be performed easily under direct vision by laparoscopic surgery. Better case selection and adequate experience in laparoscopic

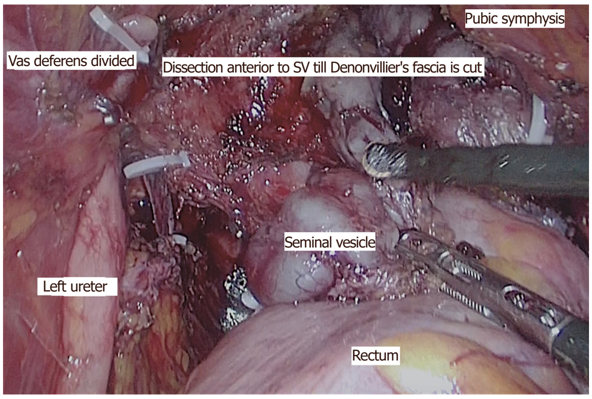

Figure 7. Laparoscopic anterior resection with seminal vesicle excision

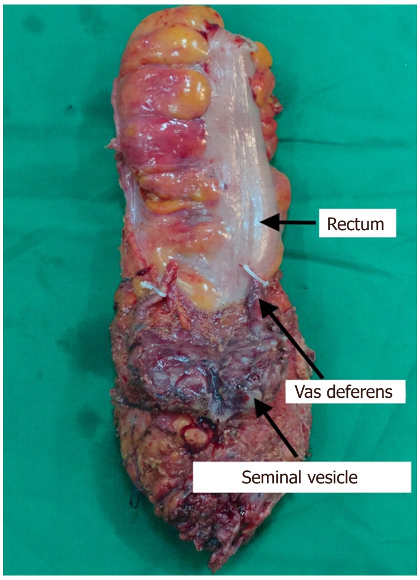

Figure 8. Specimen of laparoscopic anterior resection with seminal vesicle excision

surgery are paramount for successful laparoscopic extended resections. Nagasaki *et al.*[25] confirmed the role of laparoscopic extended resections for locally recurrent rectal cancer to achieve R0 resection.

The reports on robotic extended resections are scarce. One of the largest series of robotic extended resections was published by Shin *et al.*[74]. The study included eight prostate or seminal vesicle excisions, three partial cystectomies, and five partial vaginal wall excisions along with other multi visceral resections. There were urinary leakage in one patient and five patients developed urinary retention. R0 resection was achieved in all patients. The 5-year cumulative local recurrence rate was 3.6%. The 5-year actuarial disease-free rate was 54.6% and an OS rate was 80%. The authors confirmed that the robotic extended resection is safe and feasible with good perioperative outcomes, a low risk for conversion, a high rate of R0 resection, and acceptable long-term oncological outcomes.

ABDOMINOSACRAL RESECTION

Abdominosacral resection is required when locally advanced/recurrent rectal cancer involves presacral fascia and sacrum. Williams *et al.*[75] reported an R0 resection following laparoscopic abdominosacral

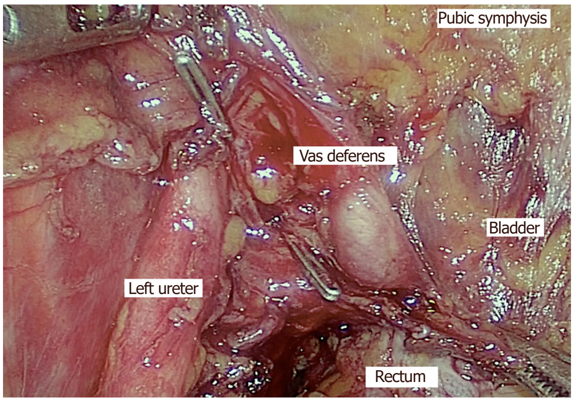

Figure 9. Laparoscopic extended resection showing distal ureter where it arches below the vas deferens

resection in three patients with locally advanced rectal cancer. After abdominal part of laparoscopic surgery, sacral resection (below S3/S4) was performed in prone position. Laparoscopic abdominosacral resection provides short-term benefits of MIS approach with negative circumferential margin[76,77]. Uemura *et al.*[78] recently reported a complete laparoscopic abdominosacral resection using a Gigli wire saw for a locally recurrent rectal cancer. The distance between the estimated line of resection (below the S4 vertebra) and sacral promontory was measured by preoperative imaging. Intraoperatively, line of resection was marked and Gigli wire was passed dorsal to sacral bone at the level of resection. Both the ends of wire were brought out through lower abdominal ports and sacrum was cut by the linear reciprocating motion of the Gigli wire saw.

This review has several limitations. There were no randomized controlled trials or prospective studies available in the current literature in context to this review. There was heterogeneity between the studies with small sample size. There were no studies with long-term follow-up to evaluate oncological outcomes. Short-term outcomes were variable due to patient selection bias and heterogeneity in the available studies.

CONCLUSIONS

The technological advances in instrumentation, advances in surgical techniques, increased surgeon experience made MIS feasible with good perioperative outcomes in b-TME/e-TME in carefully selected patients. Laparoscopic surgery has considerable learning curve and should be performed by experienced surgical teams. Robotic surgery is feasible and beneficial in complex resection in pelvis. However, evidence for long-term oncological outcomes of MIS in b-TME/e-TME is low and needs to be studied further by randomized controlled trial once enough numbers are possible in institutes with high volume rate.

DECLARATIONS

Authors' contributions

Concepts and definition of intellectual content: Kumar NAN, Saklani A
Literature search: Kumar NAN, Kammar P
Design, manuscript preparation, editing, and review: Kumar NAN, Kammar P, Saklani A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

The authors declare 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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Functional results and quality of life after transanal total mesorectal excision

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Abstract

This is a narrative review on ano-rectal, sexual, urinary, and quality of life outcomes after transanal total mesorectal excision (TME). Little is known on this topic as only a few studies are currently available in the literature. According to these, it appears that the functional results and quality of life are not substantially impaired compared with standard TME. However more data are needed to precisely assess the outcomes of this technique.

Keywords: Rectal cancer, transanal total mesorectal excision, functional results, quality of life

INTRODUCTION

Rectal resection with total mesorectal excision (TME) is considered the standard treatment for cancer located in the mid and low rectum, as it provides removal of the primary tumor together with the mesorectal lymph nodes[1]. However, TME for low rectal cancers, whether performed via an open or conventional laparoscopic approach, is technically demanding, particularly in patients with unfavourable features such as obese male patients, with a narrow pelvis or bulky tumor, where obtaining adequate resection margins can be challenging. The transanal total mesorectal excision (taTME) technique has been recently introduced to facilitate distal mobilization of the rectum and has raised great interest worldwide since it may overcome some of the limitations encountered in abdominal TME[2].

Compared to standard laparoscopic TME, taTME has potential advantages: a superior quality of the specimen with better preservation of mesorectal integrity[3,4], a better anastomotic technique[5,6], no need for an abdominal incision for specimen extraction, reduced incidence of wound problems[7], less conversions to open surgery, more sphincter-saving procedures and no impairment of oncological outcomes[8-10]. Another benefit is that the visualization of the surgical plane is improved in the more difficult part of the operation, namely the mid- and low rectum, thus allowing more accurate dissection. Potentially, this could enhance the identification of the pelvic autonomic nerves and their sparing, thus better preserving sexual and voiding functions. Chouillard *et al*.[11] compared intraoperative visualization of the neurovascular bundles of Walsh in patients undergoing standard laparoscopic TME or taTME. Bilateral visualization of the nerves was achieved in 77.8% of patients in the taTME group and in only 33.3% of patients in the standard laparoscopic TME group. Besides better visualization, in the standard TME during anterior dissection of the mesorectum an excessive traction at the level of the seminal vesicles might injure the neurovascular bundle while during the taTME procedure this traction is avoided[12]. Nevertheless taTME has also several drawbacks. Prolonged dilatation of the anal canal with the trans-anal platform, might damage the sphincter muscles[13] and a significantly longer distal resection margin has been described with taTME in several studies[13,14]. As a result the anastomosis is potentially created more distally with a higher number of handsewn colo-anal anastomosis. This may impair anorectal function. Furthermore, a dissection in a more peripheral plane could produce inadvertent neural damage, particularly within the learning phase of the procedure[15]. Finally an increased rate of urethral injury has been reported in the taTME international registry, which could lead to urinary incontinence and dysfunction[16].

FUNCTIONAL OUTCOME AFTER TME

After rectal cancer surgery a substantial number of patients may report different complaints related to bowel, sexual, and urinary functions, social relationships and psychological aspects.

Functional bowel disturbance after rectal resection affects significant numbers of rectal cancer patients[17]. Many factors have been related to bowel dysfunction such as reduced capacity of the neorectum, damage to the bowel innervation and to the anal sphincter muscles and pudendal nerves, or loss of the recto-anal inhibitory reflex[18,19]. The level of anastomosis also plays a significant role while lower anastomosis, particularly colo-anal anastomosis and intersphincteric resections, can lead to a higher risk. In an attempt to improve postoperative bowel function, the construction of a side-to-end anastomosis, a J-pouch or a coloplasty has been performed with short term functional improvement but with minimal differences after a 2-year follow-up[20]. After rectal resection approximately 60% of patients experience some degree of fecal incontinence (FI). When evaluated by anorectal manometry, significant impairment of both internal and external sphincters, as well as reduced capacity of the neorectum have been demonstrated[21].

In addition to fecal incontinence, one-third of patients complain other symptoms such as urgency, increased bowel frequency, fragmentation and soiling. These defecation disorders called “anterior resection syndrome” can seriously impact on quality of life[22]. Although the symptoms tend to improve over the first two years after surgery, a permanent impairment of anorectal function is often observed.

Genitourinary function impairment is mainly related to nerve injury during pelvic dissection. After laparoscopic or open TME the reported incidence of urinary dysfunction, including incontinence, retention and dysuria, ranges between 0% and 26%. Sexual dysfunctions have been more intensively studied in men than in women; they involve erectile and ejaculatory problems, loss of desire, diminished sexual activity and anospermia, and ranges between 11% and 38%[23-25]. In the Dutch trial, involving 1861 patients, urinary incontinence, 5 years postoperatively, was reported by 38% of patients, 72% of whom had normal urinary function before surgery. Additionally, general sexual dysfunctions 2 years after rectal cancer treatment were reported by 62% of women, and by 76% of men[26].

QUALITY OF LIFE AFTER TME

Quality of life (QoL) in rectal cancer patients is related to the presence and severity of the tumor, to surgical morbidity, to the effects of surgery on genitourinary and bowel function, and to adjuvant or neoadjuvant therapies. The relationship between postoperative functional disorders and QoL is not fully clarified and is not frequently reported in the literature; the impact of dysfunctions on well-being may vary according to patients' expectations and length of follow-up. The first studies investigating QoL after rectal cancer surgery were mainly focused on the effect of permanent stoma. Although there is a general consensus that QoL is worse after an abdominoperineal resection than after an anterior rectal resection, a recent Cochrane review failed to demonstrated a clear advantage of sphincter-saving operations over permanent colostomies[27]. In a study by Vironen *et al.*[28] assessing surgery-related adverse effects on quality of life, major bowel dysfunction impaired social functioning, while incontinence and fecal urgency also affected mental health, and general health perception. Urinary dysfunctions worsened social functioning while, among sexual dysfunctions, only a complete loss of erection but no partial dysfunction, was associated with significantly worse physical and social functioning.

INSTRUMENTS MEASURING FUNCTION AND QOL

A number of scoring systems for the assessment of symptoms after rectal cancer surgery have been created in order to objectively describe the characteristics and severity of symptoms and to compare the outcomes of different conservative and surgical treatments or to compare results of published data.

For the evaluation of continence, information on frequency and quantity of loss is fundamental[29], but the ability to defer defecation, the use of pads, the impact of symptoms on work activity or on lifestyle[30,31] or the use of specific medication[32] should be also taken into account.

For other bowel dysfunctions arising after rectal resection, a low anterior resection syndrome score (LARS score) has been created and has been recently internationally validated[22]; based on the results, three groups with no, minor and major LARS have been described. This scale is a reliable tool in clinical practice, also considering the high correlation between the LARS score and quality of life: significant differences were found between patients with no LARS and major LARS particularly in several subscales such as global health, social functioning and role functioning[33].

Concerning the assessment of quality of life, several questionnaires have been expressly created for evaluating the health status of cancer patients[34] or, more specifically, of colorectal cancer patients[35]. Postoperative QoL in cancer patients depends on many factors related to the tumor itself, to the treatments or to dysfunctions. These cancer specific questionnaires more accurately reflect the impact of all these factors on different aspects of health, since more generic questionnaires, or questionnaires for other benign anorectal conditions, might not be of sufficient sensitivity to detect differences.

A more detailed description of questionnaires employed in the assessment of functional impairment and QoL in rectal cancer patients is reported in the Supplementary Material.

ANORECTAL, SEXUAL, URINARY, AND QUALITY OF LIFE OUTCOMES AFTER TATME

At present, data on anorectal, sexual and urinary functions after taTME are scanty. There are few studies, usually involving a limited number of patients, and short follow-up. Moreover, as far as function is concerned, few comparative studies with standard TME and no randomized trial are available.

Four studies published between 2013 and 2015, reflecting the initial experience with this technique, were mainly focused on feasibility and short term surgical results, however they also tried to assess anorectal symptoms. All of them only evaluated fecal incontinence symptoms. Three employed the Wexner Incontinence score[36-38], while Atallah *et al.*[39] examined 20 patients with a telephone survey 8 weeks after ileostomy closure: most patients stated they had less than one accident per day, and one patient reported lifestyle-limiting incontinence that did not improve 12 months post-resection. In three of the studies incontinence symptoms were only evaluated after surgery[36,37,39]. In one study 6 patients completed the Wexner incontinence score one week and 6 months after surgery[38]: mean score only slightly deteriorated from 0 to 3 at 6 months after surgery and 4 months after stoma closure. A similar mean Wexner score value of 3.3 was reported by Borreca *et al*.[36] with no patient complaining of urgency symptoms. A worse anorectal function was reported by Rouanet *et al*.[37] who studied 30 patients with advanced or recurrent low rectal tumor with complex anatomical (male gender, high BMI, fatty mesorectum), or tumor characteristics (bulky anterior tumor, narrow radial margin). The patients completed the Wexner Incontinence score 12 months after stoma closure and the median score was 11. Only 40 % of patients were fully continent, while 15% and 35% reported incontinence to liquids and gas respectively; additionally 25% of the patients complained stool fragmentation.

The first study focusing more on functional results was published in 2015 and involved 52 patients with low rectal cancer, who underwent colo-anal or intersphincteric resection; the patients were evaluated at least 12 months after surgery or after stoma closure with the Wexner incontinence score questionnaire; bladder and sexual function were also evaluated. Three patients (5.7%) required a colostomy because of severe fecal incontinence after intersphincteric resection. For the remaining 49 patients without a stoma, the median Wexner score was 4 (range: 3-12), 13 patients (28%) reported stool fragmentation and difficult evacuation. Five patients (8.9%) developed postoperative urinary retention that resolved within 3 months. Deterioration of sexual function, in male patients, was reported by 22.2%, decreased potency by 2 and impotence by 2 patients (11.2%). The authors concluded that taTME does not negatively impacts on functional outcomes, however there was not a comparative group[40].

Kneist *et al*.[41] published in 2016 the first study with a comprehensive prospective assessment of urinary, sexual and intestinal function after taTME using validated instruments. The study involved 10 patients who underwent taTME with colo-anal or intersphincteric resection. Preoperative function was compared to functional outcomes at 3, 6 and 9 months, after surgery or stoma closure. A unique and added value of this study was that pelvic autonomic nerve preservation was intraoperatively assessed electrophysiologically: an electromyography of the anal sphincter and a cystomanometry were performed during electric stimulations along the pelvic walls during mesorectal dissection. All patients completed validated questionnaires assessing: urinary function (IPSS score)[42], Quality of Life (QoL Index)[43], male sexual function (IIEF score)[44]; female sexual function (FSFI)[45]; anorectal function, determined by the Wexner score[30], and by the low anterior resection syndrome (LARS) score[22]. In addition residual urine volume was evaluated. None of the patients developed pathological residual urine volumes after at least unilateral functional pelvic nerve-sparing. No significant difference in bladder function was noted nevertheless IIEF score was lower than preoperative values. Of note sexual function was already impaired in 60% of patients preoperatively. The median Wexner score deteriorated from 1 to 7 at 6 months (P = 0.029). Four patients had major LARS at 1 month but only one at 6 months, with 40% of patients categorized as having no LARS and 50% minor LARS. A worse QoL due to fecal incontinence was found in 3 out of the 10 patients, 2 of whom had a partial intersphincteric resection, and 1 suffered tumor progression. The authors' conclusion was that taTME has the potential to preserve continence, sufficient bowel function, and urogenital function. Although the study examined in a rigorous and comprehensive way all the functional outcomes, the sample size is small and there are too many confounding factors to draw any definitive conclusion[41].

The most recently published study involved 30 patients with low and medium rectal cancer[15]. The following questionnaires were completed by the patients 1 week before and 1 and 6 months after surgery: EuroQoL, (EORTC) QLQ-CR29[46], and QLQ-C30[47], LARS score. Preoperative LARS score ranged between 7.3 and 23.5, with the mean score being 15.4; a significative increase to 35.7 was recorded at 1 month, but after 6 months, it fell to 21.7, with no significative difference with respect to preoperative value; 33% of patients

Table 1. Studies evaluating function and QoL in taTME

Studies	No. of patients	Tumor characteristics	Function	Instruments	Time of evaluation
Rouanet *et al*.[37], 2013	21	Advanced or recurrent cancer, complex anatomy or tumor	FI	WS	12 months after stoma closure
Atallah *et al*.[39], 2014	20	Low, mid locally advanced or distal rectal cancer + complex anatomy	FI	telephone survey	8 weeks after stoma closure
Elmore *et al*.[38], 2015	6	Low, mid rectal cancer	FI	WS	Pre-operation, 6 months post
Kneist *et al*.[41], 2016	10	Low rectal cancer, colo-anal anastomosis or partial inter-sphincteric resection	Bowel, urinary, sexual functions, QoL	IPSS, IIEF, FSFI, LARS, RUV, WS, QoL index	Pre-operation , 3, 6, 9 months post-operation
Koedam *et al*.[15], 2017	30	Any rectal cancer, with primary anastomosis	Bowel, urinary, sexual functions, QoL	EQ-5D, QLQ-C30 QLQ-CR29, LARS	Pre-operation, 1, 6 months post-operation
Borreca *et al*.[36], 2015	18*	Any rectal cancer	FI	WS	Post operation
Tuech *et al*.[40], 2015	52	Low rectal cancer, colo-anal anastomosis or intersphincteric resection	Bowel, urinary, sexual (male) function	WS, interview	Post operation

*Total number of patients, only patients who had their stoma closed were evaluated but the number is not reported. WS: Jorge-Wexner score; IPSS: international prostate symptom score; IIEF: international index of erectile function; FSFI: female sexual function index; LARS: low anterior resection syndrome score; FI: fecal incontinence; QoL: quality of life; taTME: transanal total mesorectal excision

had major LARS but no colostomies were required. Both the overall QoL and the colorectal cancer specific QoL score significatively decreased one month after surgery, but most outcomes returned to baseline after 6 months, except for social function and anal pain. Urinary symptoms, incontinence, increased frequency or dysuria, did not change significantly after taTME. Sexual function significantly worsened at 1 month postoperatively, but returned to the same level as before surgery at 6 months. The authors' conclusion was that taTME is associated with acceptable QoL and functional outcomes comparable with conventional laparoscopic TME. Table 1 summarizes the articles dealing with functional results in taTME.

CONCLUSIONS

Given the limitations of the existing studies larger studies have been advocated. Several studies exploring this novel surgical technique and the functional sequelae have been registered into clinicaltrial.gov, and some of them are already recruiting patients. Among them the COLOR III trial[48], an international, multicentre, randomized trial, is expected to enrol more than 1000 patients in 4 years. In addition to clinical and oncological parameters, quality of life and functional outcomes will be assessed at 1, 3, 6, 12, 24 and 36 months after surgery by means of specific questionnaires.

In conclusion, published data concerning anorectal function, urinary and sexual function, and quality of life after taTME are still scarce and comparative data are lacking. Based on the few available studies, taTME does not seem to substantially impair functional and quality of life outcomes when compared to laparoscopic abdominal TME. However further studies are needed to confirm these results; the ongoing studies and particularly the COLOR III trial, will hopefully provide more firm updates for a more accurate assessment of this promising technique.

DECLARATIONS

Author's contribution

The author solely contributed to the article.

Availability of data and materials

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Conflicts of interest
The author declares that there are no conflicts of interest.

Ethical approval and consent to participate
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Mini-invasive Surgery

Original Article

Laparoscopic and endoscopic cooperative surgery for non-ampullary duodenal epithelial neoplasms

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Abstract

Aim: We herein describe our initial experience of laparoscopic and endoscopic cooperative surgery (LECS) for non-ampullary duodenal epithelial neoplasms (NADENs) and reveal its clinical significance.

Methods: This study included 5 consecutive patients treated by LECS for NADENs between April 2015 and January 2016 in our hospital. For surgery, R0-resection of NADENs was accomplished by endoscopic submucosal dissection (ESD), and the mucosal defect resulting from ESD was subsequently repaired by laparoscopic seromuscular suture and endoscopic clipping. Clinical records were reviewed retrospectively.

Results: LECS was accomplished in four patients. There was a case of open conversion due to the relatively large mucosal defect resulting from ESD. In the postoperative course, no serious complications, including intra- and postoperative bleeding and delayed perforation, were noted. The duodenal stenosis occurred in the case of open conversion but was treated by repeated endoscopic balloon dilatation. Of the five lesions of NADENs, there were three adenomas and two adenocarcinomas confined in the mucosa. To date, no tumor recurrence was observed during the postoperative course.

Conclusion: LECS is a promising procedure of choice in the treatment of NADENs, facilitating early resumption of both food intake and full daily activity in the postoperative course.

Keywords: Endoscopic submucosal dissection, laparoscopic and endoscopic cooperative surgery, non-ampullary duodenal epithelial neoplasms

INTRODUCTION

Recent advances in gastrointestinal endoscopic technology and diagnostic skills have led to increased occurrence of asymptomatic non-ampullary duodenal epithelial neoplasms (NADENs) in daily clinical practice[1-3]. Either endoscopic mucosal resection (EMR) or submucosal dissection (ESD) has occasionally been indicated in the treatment of NADENs, but the procedure remains technically challenging, given that expertise in both meticulous dissection and subsequent repair is required in the narrow lumen of the duodenum[2-5]. In addition, the prevention of bleeding and perforation during and after the procedure is pivotal, given that the incidence of these serious complications is relatively frequent in ESD for NADENs[4-6].

Laparoscopic and endoscopic cooperative surgery (LECS) was initially invented for the purpose of less invasive surgery for gastric non-epithelial neoplasms[7] but later employed to overcome the limitation of ESD for early gastric cancer (e.g., non-exposed wall inversion surgery (NEWS[8]), a combination of laparoscopic and endoscopic approaches to neoplasia using non-exposure techniques (CLEAN-NET[9]). Similarly, recent reports demonstrated that LECS offers a promising procedure of choice to facilitate less invasive surgery in the treatment of NADENs[10-15], but the clinical evidence verifying its efficacy remains limited. In this report, we sought to investigate our initial experience of LECS for NADENs and further reveal its clinical significance. Our LECS procedure including ESD and subsequent laparoscopic and endoscopic repair may extend the indication of ESD and improve its safety in the treatment of NADENs.

METHODS

Five consecutive patients with the diagnosis of NADENs between April 2015 and January 2016 were included in this study. All of the patients were referred to the department of surgery by the gastroenterologists. LECS for NADENs was indicated for these patients following routine preoperative examination including esophagogastroduodenoscopy with concomitant biopsy, endoscopic ultrasonography (EUS), upper GI series and computed tomography (CT). Gastroenterologists and surgeons had deliberate discussion to determine the surgery indication for all of patients. In the discussion, special attention was given to the distance between NADENs and Vater papilla obtained from upper GI series images in view of both the prevention of the injury to Vater papilla and the security of the resection margin at least 10 mm away from Vater papilla. Epithelial neoplasms confined in the mucosa at the risk of malignancy were eligible for treatment. In principle, NADENs located in the duodenal wall side of the pancreas head were preoperatively contraindicated for LECS, given that laparoscopic suture repair following ESD was considered to be rather demanding. All of the patients consequently provided written informed consent prior to surgery. Clinical records were reviewed retrospectively. Clinical outcomes included operation time, blood loss, intra- and postoperative complications, and length of postoperative hospital stay. Postoperative complications were graded according to the Clavien-Dindo Classification (C-D: Grade[16]). All patients were followed up in the outpatient clinic after the discharge. The follow-up examination included the endoscopy during the first postoperative year. In cases with malignancy in the final diagnosis, CT was also periodically performed in the outpatient clinic.

LECS procedure for NADENs

The surgery of LECS for NADENs was performed by a single surgeon (HT) with the certification of Japan Society for Endoscopic Surgery. The patient was placed in a supine position with both legs apart under general anesthesia. A total of five ports were inserted in the abdomen, as described in Figure 1, and the pneumoperitoneum was created and maintained at approximately 8 to 10 mmHg. The operative field was visualized by 3-dimensional imaging systems equipped with a 10 mm flexible scope (Olympus, Tokyo, Japan) through the infraumbilical port. The infrapyloric region was reached by the dissection of the greater omentum in the vicinity of the transverse colon with an ultrasonically activated scalpel. Following the adequate mobilization of the duodenum, the upper jejunum around 10-20 cm away from Treiz ligament was

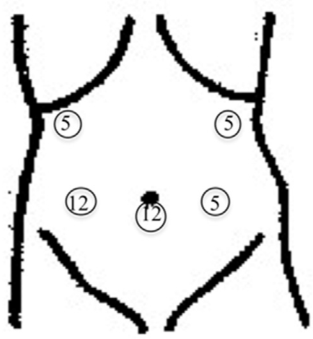

Figure 1. Port site. The value in the circle indicates the size of each port inserted in the abdomen

temporarily occluded with the laparoscopic intestinal clamper, and ESD was commenced by the gastroenterologist (KH with the certification of Japan Gastroenterological Endoscopy Society). The localization of NADENs was confirmed endoscopically and thereafter treated by regular ESD. Considerable attention was given to avoid Vater papilla injury during the procedure. The mucosa approximately 2-3 mm away from NADENs was circumferentially incised with either a flush knife or clutch cutter after local injection of the sodium hyaluronate solution around NADENs. Subsequently, the dissection was meticulously made, and the specimen was contained in the pouch and retrieved orally. Endoscopic dye injection (either indigocarmine or indocyanine green) to the ulcer bed enabled the immediate identification and repair of the mucosal defect from serosal side under laparoscopy. Intracorporeal-interrupted seromuscular sutures with 4-0 PDS (Johnson & Johnson, Cincinnati, OH) were made in perpendicular direction to the long axis of the duodenum. In addition, the mucosal defect was repaired with clips under endoscopy. Airtightness in the suture line was confirmed by sufficient inflation of the duodenum by endoscopy, and the laparoscopic intestinal clamper was finally retrieved before the release of the pneumoperitoneum.

RESULTS

Patient characteristics, preoperative and pathological data are presented in Table 1. This study included four males and one female, and the age at surgery ranged from 41 to 69 years old. In preoperative data, none of the five NADENs was malignant in biopsy and all of the lesions were supposed to be confined in the mucosa in EUS. In CT, neither regional lymph node swelling nor distant metastasis was shown in all of the patients. Of the five NADENs, there were three adenomas and two adenocarcinomas confined in the mucosa based on the pathological reports in the postoperative course. All of the lesions treated by LECS were located in the second portion of the duodenum. The distance between NADENs and Vater papilla was measured in the upper-GI series images in all of the patients and ranged from 14 to 32 mm. In cases 2 and 3, NADENs were observed in the vicinity of Vater papilla (15 mm in case 2, 14 mm in case 3), but the indication of LECS was approved, given that the lesions were not located in contact with the pancreas head. The representative NADENs images from case 3 are presented in Figure 2. The section of the LECS for NADENs procedure is presented in Figure 3. The operative results are presented in Table 2. The total operation time ranged from 152 to 552 (mean 264) min. In case 5, the relatively large mucosal defect resulting from ESD (tumor size: 54 mm × 47 mm in Table 1) for NADENs resulted in the only open conversion during the procedure in this study [Table 2]. Following the laparotomy, full thickness suture repair of the duodenum was performed under the direct vision. In ESD, R0-resection was accomplished in all of the patients. The active bleeding during ESD was mainly treated with the electrocoagulation. In case 1, microperforation occurred during ESD, but was successfully repaired by subsequent clipping under endoscopy. With regard to postoperative complications, the duodenal stenosis in case 5 was treated by endoscopic balloon dilatation for four times during the hospital stay (C-D: Grade IIIa), but bleeding and perforation were not noted during the procedure and postoperative course. In all of the patients treated with LECS for

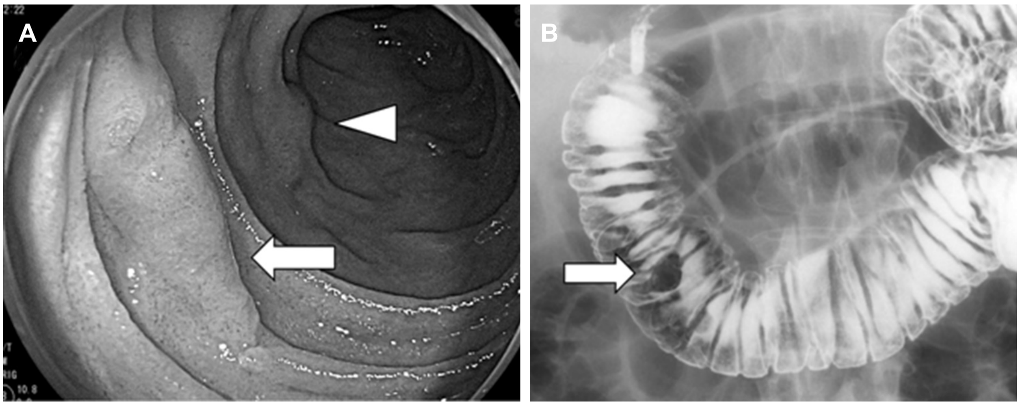

Figure 2. Representative images of NADENs from case 3. (A) Endoscopic image, arrow: NADENs, arrowhead: Brunner gland; (B) upper GI series images, arrow: NADENs

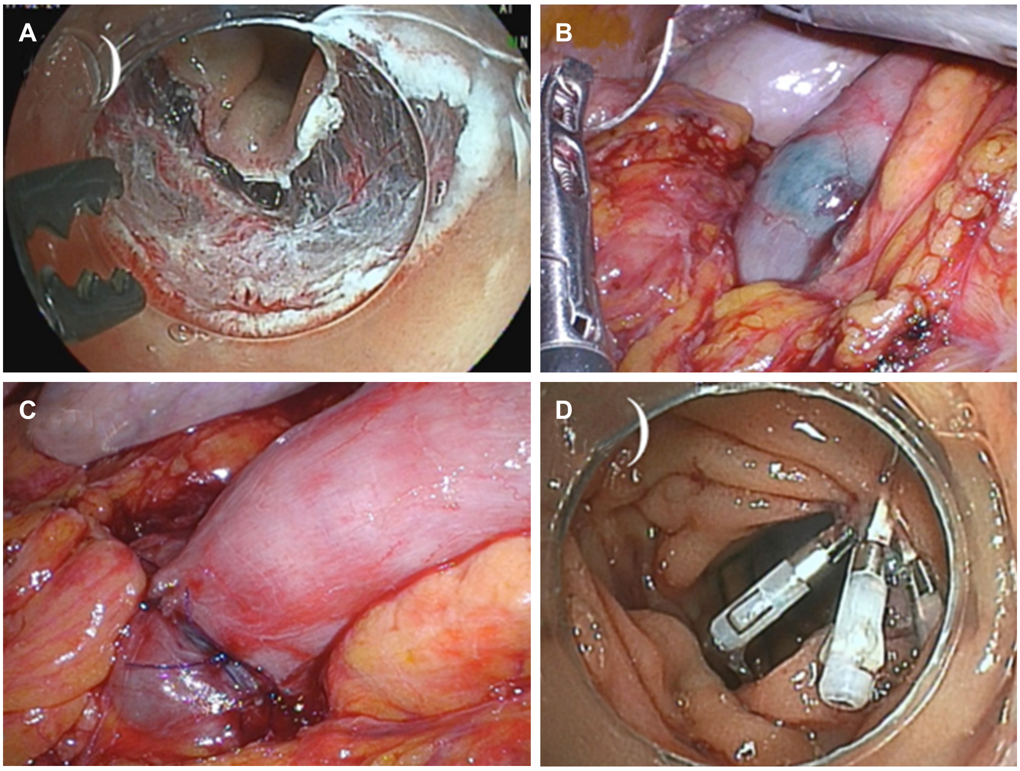

Figure 3. Operative findings. (A) The mucosal defect resulting from ESD; (B) the endoscopic dye injected into the ulcer bed allowed for the immediate identification of the duodenal lesion under laparoscopy; (C) intracorporeal interrupted seromuscular sutures were made along the right direction of the long axis of the duodenum; (D) the mucosal defect was further repaired with clips under endoscopy

NADENs, both vertical and horizontal margins of the specimen were free of tumor cells. In the postoperative course, the patients with the exception of case 5 resumed food intake on postoperative days (POD) 3-5 and full daily activity on the day of discharge. In case 5, the liquid diet was allowed to take on POD 38 and normal diet on POD47. The patient resumed full daily activity at the discharge of POD 49. In the outpatient clinic, follow-up endoscopy was performed for all of the patients during the first postoperative year, and CT was performed for the two patients with adenocarcinomas for every 6 months. To date, neither tumor recurrence nor metastasis was noted in any of the patients.

Table 1. Patient characteristics, preoperative and pathological data

Case No.	Age	Gender	Tumor location	Distance from papilla (mm)	CT	EUS	Biopsy	Macro-scopic appear-ance	Postop pathology	Tumor size (mm)	Specimen size (mm)
1	54	Male	2nd portion	32	np	Mucosa	Adenma	II c	Adenoma	12 × 7	22 × 15
2	41	Male	2nd portion	15	np	Mucosa	Adenma	II c	Adenoma	21 × 17	31 × 26
3	57	Male	2nd portion	14	np	Mucosa	Atypia	II a	Adeno-carcinoma	16 × 9	29 × 19
4	69	Female	2nd portion	21	np	Mucosa	Adenma	II c + II a	Adenoma	14 × 6	19 × 14
5	50	Male	2nd portion	29	np	Mucosa	Adenma	II a	Adeno-carcinoma	54 × 47	68 × 55

In CT, np indicates neither significant regional lymph node swelling nor distant metastasis. Case 5 was the only case of open conversion. Three adenomas and two adenocarcinomas were confined in the mucosa

Table 2. Operative results

Case No.	ESD/total op time (min)	Blood loss (mL)	Intraop complications	R0-resection	Repair	Postop complications	Postop hospital stay (days)
1	98/228	10	Micro-perforation	Yes	Suture + clips	None	7
2	49/152	5	None	Yes	Suture + clips	None	9
3	56/187	30	None	Yes	Suture + clips	None	8
4	26/202	5	None	Yes	Suture + clips	None	8
5	252/552	100	None	Yes	Suture	Stenosis	49

Micro-perforation during ESD was immediately repaired with clips under endoscopy. Duodenal stenosis occurred in the case of open conversion but was treated by repeated endoscopic balloon dilatation. ESD: endoscopic submucosal dissection

Table 3. Previous reports of LECS for NADENs

Year	Author	No.	Tumor size (mean:mm)	Repair	Op time (mean; min)	No. of cancer (%)	Conversion	No. of postop complications (%)
2010	Sakon *et al.*[10]	2	19	Suture	168	0 (0)	None	0 (0)
2010	Tsujimoto *et al.*[11]	2	21.5	Suture	116	0 (0) *	None	0 (0)
2014	Ohata *et al.*[12]	22	13.3	Suture	133	6 (27.3)	None	5 (22.7)
2015	Irino *et al.*[13]	3	17	Suture	234	3 (100)	None	1 (33.3)
2015	Kyuno *et al.*[14]	2	12.5	Suture	131	0 (0)	None	0 (0)
2016	Ichikawa *et al.*[15]	12	22	Suture	322	10 (83.3)	None	2 (16.7)
2018	Ojima *et al.*[20]	18	18 (median)	Suture	116.5 (median)	4 (38.9)	None	0 (0)
	Our study	5	23.4	Suture + clips	264	2 (40)	Yes	1 (20)

*The final diagnosis of both cases was carcinoid tumors. No. of cancer (%) indicates the number of cases with cancer in the final diagnosis and its rate of incidence. No. of postoperative complications (%) indicates the number of cases with postoperative complications and its rate of incidence. Postoperative complications were occasionally documented in previous reports, but treated conservatively (C-D: Grade II or IIIa). LECS: laparoscopic and endoscopic cooperative surgery; NADENs: non-ampullary duodenal epithelial neoplasms; C-D: Clavien-Dindo Classification

DISCUSSION

In this study, we present our initial experience of LECS for NADENs, which was accomplished in four out of the consecutive five cases. We did not experience serious intra- and postoperative complications (> C-D: Grade IIIb) or tumor recurrence, thereby suggesting the feasibility of our LECS procedure for NADENs, although the results from our small number of case series study remain limited. In our series of cases successfully treated by LECS, early resumption of food intake and full daily activity approximately one week in the postoperative course demonstrated the reduced invasiveness of our LECS procedure for NADENs. There was one case of open conversion due to the relatively large mucosal defect (tumor size: 54 mm × 47 mm in case 5) resulting from ESD in this study, implying the limitation of the indication of our procedure for LECS for NADENs. Abe *et al.*[17] reported the successful treatment of duodenal GIST, 62 mm in diameter by laparoscopy-assisted full-thickness resection, where both resection of the lesion and subsequent repair was performed manually under the 5 to 7 cm upper median laparotomy, suggesting the promising alternative to our LECS procedure for large NADENs.

In the literature[10-15], a total seven authors reported a series of LECS for NADENs where the lesions were treated by either ESD and subsequent laparoscopic repair or endoscopy-assisted laparoscopic full-thickness resection and repair without any serious intra- and postoperative complications, corresponding to our results [Table 3]. In those reports, surgery was occasionally performed for adenocarcinomas confined in the mucosa, but no tumor recurrence was noted in the postoperative course, revealing the feasibility of the indication of LECS for NADENs. Regarding the size of NADENs successfully treated with LECS, the mean diameter ranged from 13.3 to 22 mm [Table 3]. From our experience of only one conversion involving a tumor that was 54 mm in diameter, LECS might be accomplished for NADENs within approximately 30 mm in diameter and at least 10 mm away from Vater papilla.

Our LECS procedure for NADENs is consistent with the previous reports, demonstrating ESD and subsequent laparoscopic repair in the treatment of NADENs[13,14]. Complete resection of the lesions by ESD without micro-perforation theoretically enables the avoidance of tumor dissemination in the peritoneal cavity, where the precise preoperative evaluation of the depth of NADENs is inevitable. Furthermore, postoperative analysis of pathological results is critical, given that additional surgery could be required in cases involving margins or vertical invasion beyond the submucosal layer of malignant lesions. Long-term follow-up for patients with malignant results are warranted to verify the oncological feasibility of LECS for NADENs.

Exposure of the epithelial injury in the duodenum to bile and pancreatic juice impairs tissue regeneration[18,19]. Consequently, repair of the mucosal defect resulting from ESD is critical for the prevention of postoperative complications in LECS for NADENs. Compared with previous reports[13,14], our procedure for LECS for NADENs is novel in terms of the repair procedure after ESD consisting of the combination of laparoscopic hand-sewn seromuscular suture and endoscopic clipping, enabling the closure of the mucosal defect from both inside and outside the duodenum [Figure 3]. The anticipation of laparoscopic hand-sewn seromuscular sutures contributed to the reduction of the mucosal defect and therefore facilitated subsequent endoscopic clipping, compared with immediate clipping after ESD. In our results, immediate or delayed bleeding and perforation did not occur, revealing the feasibility of repair using LECS for NADENs. The future prevalence of robotic surgery may facilitate the laparoscopic suturing in LECS for NADENs.

Ojima *et al.*[20] recently reported the operative results of LECS superior to ESD for the treatment of NADENs in the comparative study. They showed the statistically decreased incidence of any postoperative complications including bleeding and perforation in LECS, demonstrating LECS contributed to the improvement in the safety during and after ESD for the treatment of NADENs. To date, clinical data regarding LECS for NADENs derived from the short-term outcomes. Therefore, it should be reminded the long-term oncological outcomes remain to be verified for the establishment of LECS for NADENs. For the moment, the indication of LECS for NADENs requires deliberate consideration before the surgery and should be limited to NADENs at low-risk of biological aggressiveness.

In conclusion, LECS is a promising procedure of choice in the treatment of NADENs, facilitating early resumption of both food intake and full daily activity in the postoperative course. Further accumulation of clinical evidence is warranted for the establishment of the treatment strategy and obtaining long-term results of LECS for NADENs.

DECLARATIONS

Authors' contributions

Study concept and design, manuscript preparation: Toma H, Haraguchi K, Eguchi T

Data collection, literature research: Toma H
Analysis and interpretation of results: Toma H, Haraguchi K, Fujii K, Kobarai T, Hirota I, Eguchi T

Availability of data and materials
The data is presented and kept by the author and is available for scrutiny.

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None.

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/institutional review board in our hospital (No2017-33). Informed consent was obtained from all patients for being included in the study.

Consent for publication
Not applicable.

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Mini-invasive Surgery

Review

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The role of transanal total mesorectal excision in rectal surgery

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Abstract
Transanal total mesorectal excision (TaTME) is the newest approach for the resection of rectal cancer, according to the principles of TME. The evolution of TaTME started almost 40 years ago and is a combination of several important developments in both micro-endoscopic surgery and transanal surgery. The preliminary clinical data have revealed acceptable TME quality. Clinical trials to determine the long-term oncological results are still in process. In order to master TaTME, the surgeon should be an expert in laparoscopic rectal surgery as well as transanal microsurgery and follow a stepwise training approach. Robotic TaTME using a single-port robotic system is a promising future development.

Keywords: Transanal total mesorectal excision, rectal cancer, single port robotic proctectomy, transanal total mesorectal incision training

INTRODUCTION AND HISTORY

The evolution of transanal total mesorectal excision (TaTME) began with the introduction of TME by Heald *et al.*[1]. In 1982, they showed a reduction in the local recurrence rate from 40% to < 10% by employing TME. Components of TME include a complete or near complete rather than an incomplete mesorectal specimen, tumor-free circumferential resection margins (CRM), a tumor-free distal resection margin (DRM), and the assessment of ≥ 12 lymph nodes. Initially, the operation was done in an open, trans-abdominal approach. In 1991, Marks *et al.*[2] presented the transabdominal-transanal (TATA) approach to low rectal cancer. Dr. Marks' rationale was that the transanal approach allows the surgeon to achieve distal resection margins under direct visualization and facilitates distal dissection[2]. The next step in the evolution of TaTME was the introduction of transanal endoscopic surgery (TEM). In 1992, Buess *et al.*[3] presented their experience with TEM, which utilizes a 40-mm operating rectoscope sealed with an airtight face piece. Carbon dioxide is constantly infused, thereby distending the rectum and maintaining visibility. A variety of operating instruments can be inserted through the face piece to resect adenomas and selected early carcinomas of the mid and upper rectum[3]. In 2010, Sylla *et al.*[4] presented the first case of TaTME using TEM and laparoscopy that had been performed in a 76-year-old patient with a T2N2 rectal cancer treated with preoperative chemoradiation. The specimen was transanally transected followed by a hand sewn coloanal anastomosis. TEM was not widely adopted due to its high costs, technical complexity and the long learning curve. However, Maya *et al.*[5] showed by Cussum analysis that the learning curve for TEM is associated with a significant decrease in operative time after only four cases.

Atallah *et al.*[6,7] presented the use of transanal single port laparoscopy through the anal canal (transanal minimally invasive surgery; TAMIS). A single-incision laparoscopic surgery port was introduced into the anal canal to gain endoscopic access to the rectum, pneumorectum was established, and transanal excision was performed using laparoscopic instruments.

TaTME combines the TAMIS and trans-abdominal approaches in order to achieve TME. Several potential advantages have been postulated. Atallah was the first to describe this combination of techniques including a detailed video and the results of the 20 first cases[8,9]. Rectal distention with CO_2 combined with magnified optics permits excellent visualization of tissue planes. Easier access to the low rectum may aid the surgeon with better quality TME and precise selection of the distal resection margin under direct visualization helps ensure an adequate margin. TaTME may potentially be a safer anastomosis by avoiding the multiple stapler firings often required in the abdominal approach and may result in higher rates of sphincter preserving surgery. Finally, the two-team approach can shorten the length of surgery.

CLINICAL TRIALS

Lacy *et al.*[10] reported a series of 140 patients who underwent TaTME for rectal cancer. The mean operative time was 166 min and there were no conversions or intraoperative complications. Macroscopic quality assessment of the resected specimen was complete in 97.1% and near complete in 2.1%. Thirty-day morbidity was minor (Clavien-Dindo I-II) in 24.2% and major (Clavien-Dindo III-IV) in 10%, and no mortality occurred within the first 30 days. The mean follow-up was 15 months, with a 2.3% local recurrence rate and a 7.6% rate of systemic recurrence.

De Lacy *et al.*[11] subsequently reported the pathological results of 186 patients who underwent TaTME for low (37%) or mid (63%) rectal cancer. Mesorectal resection quality was complete in 95.7%, near complete in 1.6%, and incomplete in 1.1%. Overall positive CRM and DRM were 8.1% and 3.2%, respectively. The composite of complete mesorectal excision, negative CRM, and negative DRM was achieved in 88.1% of patients.

Penna *et al.*[12] reported the short-term clinical and oncological results of the first 720 patients on behalf of the International Registry for TaTME. Seven hundred and twenty consecutive patients from 66 registered units in 23 countries included 634 patients with rectal cancer and 86 with benign pathology. Conversion to open surgery was 6.3% and the mesorectum was complete in 86%, near complete in 11%, and incomplete in 4%. The R1 resection rate was 2.7%. Post-operative morbidity and mortality were 32.6% and 0.5%, respectively. Risk factors for poor specimen (incomplete specimen, perforation, R1 resection) on multivariate analysis were positive CRMs on preoperative MRI and very low rectal tumors (< 2 cm from anal verge).

Using the same TaTME registry, Penna *et al.*[13] reported the incidence and risk factors for anastomotic failure in 1594 patients who underwent TaTME, 96.6% of which were performed for cancer and the rest for benign pathology. The overall anastomotic failure rate was 15.7% including early leak (7.8%), delayed leak (2.0%), pelvic abscess (4.7%), anastomotic fistula (0.8%), chronic sinus (0.9%), and anastomotic stricture (3.6%). Independent risk factors of anastomotic failure were male sex, obesity, smoking, diabetes mellitus, tumors > 25 mm, excessive intraoperative blood loss, manual anastomosis, and prolonged operative time.

Koedam *et al.*[14] assessed the patient-reported quality of life of 30 consecutive patients who underwent TaTME for rectal cancer. Quality of life was assessed by three questionnaires: Overall Quality of Life (EQ-5D-3L), Colorectal Cancer Specific Quality of Life (EORTC: QLQ-C30 and QLQ-CR29) and Anterior Resection Syndrome (LARS) scale. Outcomes of the questionnaires at 1 and 6 months were compared with preoperative (baseline) values. Deterioration for all domains was mainly observed at 1 month after surgery compared to baseline, but most outcomes had returned to baseline at 6 months. Social function and anal pain remained significantly worse at 6 months compared to baseline. Major LARS (score > 30) was 33% at 6 months after ileostomy closure. End colostomies were not required in any patients. The authors concluded that TaTME is associated with acceptable quality of life and functional outcome at 6 months after surgery comparable to published results after conventional laparoscopic low anterior resection.

Marks *et al.*[15] reported the long-term outcomes of 373 patients with rectal cancer underwent TaTME. Ninety six percent of TME specimens were complete/near complete, 94% had a negative circumferential resection margin, and 98.6% had a negative distal margin. Perioperative morbidity and mortality rates were 13.4% and 0.3%, respectively. The median follow up was 5.5 years. Overall local recurrence, distal metastasis, and 5-year survival was 7.4%, 19.5%, and 90%, respectively.

In a case matched study that included 300 patients, Perdawood *et al.*[16] compared TaTME (n = 100), laparoscopic TME (LaTME; n = 100), and open TME (OpTME; n = 100). The authors reported that TME resulted in lower rates of incomplete TME specimens than LaTME, but not OpTME (P = 0.016, P = 0.750, respectively). The rates of CRM involvement, mean CRM distance, and the percentages of successful surgery were comparable among the three groups (P = 0.368). The conversion to open surgery occurred only in the LaTME group. TaTME resulted in shorter operation time and less blood loss than the other two groups (P < 0.001 and P < 0.001). Hospital stay was shorter in the TaTME group (P = 0.002); complication rate and mortality were comparable among the groups.

The COLOR III randomized controlled trial is being conducted to evaluate the role of TaTME in rectal cancer and to assess oncological outcomes. It has been designed to compare short- and long-term outcomes of transanal and laparoscopic TME for mid and low rectal cancer. A total of 1098 consecutive patients scheduled for resection of a mid or low rectal carcinoma will be included. The distal border of the tumor has to be within 10 cm of the anal verge on MRI scan. Exclusion criteria are T1 tumors that can be treated by local excision, tumors with ingrowth in the internal sphincter or levator ani muscle, and all T4 tumors. All participating centers in the COLOR III trial will keep the coordinating center informed of all patients presenting with rectal cancer[17].

The ETAP-GRECCAR 11 randomized controlled trial is also comparing TaTME to laparoscopic TME. Patients with T3 lower-third rectal adenocarcinomas for whom conservative surgery with manual coloanal anastomosis is planned will be recruited. The study is designed as a non-inferiority trial with a main criterion of R0/R1 resection. The inclusion period will be 3 years, and every patient will be followed for 3 years. The number of patients needed is 226[18].

The US Multicenter study of TaTME with laparoscopic assistance for rectal cancer is a single arm feasibility trial sponsored by the Society of American Gastrointestinal and Endoscopic Surgeons and the American Society of Colon and Rectal Surgeons. The primary investigator, Patricia Sylla, aims to enroll 100 patients from 11 sites.

TRAINING PROGRAM

Although the early results from the international TaTME registry are encouraging, the participating surgeons encountered intraoperative complications and difficulties in up to 40% of procedures. These difficulties include unstable pneumorectum, ineffective smoke evacuation, and difficulty developing the correct plane. The specific intraoperative complications associated with TaTME included wrong plane dissection, which may cause presacral bleeding if the dissection plane is too posterior, or injury to the hypogastric nerve bundles if the dissection plane is too lateral. The membranous urethra in males is also vulnerable when dissection is too anterior. Those specific complications and difficulties highlight the need for structured and accredited training program. Several authors have addressed the proper training pathway to the incorporation of TaTME into clinical practice[19-25].

McLemore *et al*.[24] developed 6 key elements for the safe practice of TaTME. The authors recommended expertise in TME, laparoscopic colorectal surgery, transanal minimally invasive surgery, and intersphincteric dissection. Appropriately qualified individuals should then practice in cadaver models and enter all data in a clinical registry.

Francis *et al*.[22] conducted a consensus agreement from 207 colorectal surgeons across 18 countries including 52 TaTME specialists. They recommended that prerequisites to learn TaTME should include 3 factors: the trainee, the mentor, and the training facility. The trainee must be an accredited laparoscopic colorectal surgeon with experience of more than 30 laparoscopic TME cases, more than 5 TEM/TAMIS cases, and that the anticipated volume of TaTME cases will be more than 20 per year. The mentor must have performed at least 30 TaTMEs, is experienced in cadaveric training, and has at least two publications per year in the field of TaTME. The training facility should have a cadaveric lab and at least 10 trainees and at least 2 courses per year. For the training curriculum, the authors' recommendation includes 4 stages: self-learning, cadaver workshop, proctorship of the initial 5-10 cases, and, finally, independent practice with continued collection input into the registry.

Koedam *et al*.[26] evaluated the learning curve of TaTME in 138 patients with rectal cancer over a 60-month period. The authors reported improvement in postoperative outcomes after the first 40 patients, showing a decrease in major postoperative complications from 47.5% to 17.5% and leakage rate from 27.5% to 5%. In addition, the mean operative time (42 min) and conversion rate (from 10% to 0%) was lower after transitioning to a two-team approach, although neither endpoint decreased with experience.

PRESENT AND FUTURE

Anatomical factors that may make TaTME a preferred approach for rectal cancer include male gender, low cancers, narrow pelvis, high body mass index, and distorted tissue planes due to neoadjuvant radiotherapy[27-29]. Although the use of TaTME seems clearly advantageous for the treatment of mid and low rectal cancer, there are potential advantages to its use in upper rectal cancer, above the peritoneal reflection. Early in the learning curve it is easier to perform TaTME in higher tumors and use those cases in order to gain experience in TaTME for the more challenging, distal cancer cases. The second reason to approach upper rectum cancer transanally is the fact that the rectal specimen is of better quality in TaTME approach[30,31]. TaTME may also serve as a useful platform for proctectomy for benign diseases such as inflammatory bowel disease requiring proctectomy, rectal stricture, radiation proctitis, and Hartmann's procedure reversal.

Leo *et al*.[32] reported their experience of 16 total proctocolectomies and ileal pouch anal anastomoses (TPC + IPAA) for refractory mucosal ulcerative colitis using TaTME-assisted single port laparoscopy. The median operative time was 247 (185-470) min and the overall conversion rate to open surgery was 18.7%. The 30-

day surgical complication rate was 37.5% (Clavien-Dindo 1 in four patients, 2 in one patient and 3 in one patient who developed anastomotic leak). Carvello *et al*[33] reported a case of TaTME assisted laparoscopic TPC + IPAA for familial adenomatous polyposis (FAP) with satisfactory results. Ambe *et al*.[34] reported their experience with 8 patients who underwent TaTME assisted laparoscopic TPC + IPAA for FAP. In all cases, surgery was successfully completed using TaTME and no perioperative complications were recorded. Trépanier *et al*.[35] described their technique and experience with 10 patients who underwent reversal of Hartmann's procedure using combined laparoscopic and TaTME approaches. Indications for Hartmann's procedure were complicated diverticulitis, anastomotic leak, and rectosigmoid cancer. Reconstruction was achieved in all patients. One low colorectal anastomosis was hand sewn and the other 9 were stapled. Diverting loop ileostomies were created in five patients and all were closed during the following year. One case required hand-assistance but there was no conversion to open surgery. Three patients had a total of four post-operative complications, none of whom required reoperation.

Robotic technology includes 3-D optical visualization, ambidextrous movements, a tremor filter, and more degrees of freedom of the effector tip movement than standard instruments. These theoretical benefits may be of specific significance in confined spaces. Recently, Intuitive Surgical (Sunnyvale, California) launched the da Vinci® single port platform. The device combines a single site port with flexible robotic arms and instruments and improved ergonomics. Its use has mainly been described in gallbladder resections, gynecological operations, and urological procedures[36-39]. Jiménez-Rodríguez *et al*[38] reported two cases of robotic low anterior resection with reduced ports, using the single-port robotic platform. There were no intraoperative complications and the pathology report showed complete TME specimens[38]. Atallah et al reported the first clinical case of robotic transanal TME in a patient with a T3N1 rectal tumor located 4 cm from the anal verge. There were no complications, negative distal and circumferential margins were achieved, and the specimen quality was near-complete[40]. Verheijen *et al*.[41] reported their first case of robotic TaTME without complications and histology showed a complete mesorectal excision with free distal and circumferential margins. Marks *et al*[42]. reported the successful transanal use of the single-port system robotic platform (SPS) on four cadavers. There were no piecemeal or fragmented resections and, subjectively, closure was deemed good-to-excellent in all cases. Surgeon assessment of setup and performance of the SPS was excellent in all cases[42,43]. Kuo *et al*.[44] reported the largest series to date of 15 consecutive patients with ultra-low rectal tumors who underwent robotic TaTME followed by trans-abdominal robotic single port proctectomy and one additional port. The median number of lymph nodes harvested was 12. All patients had negative circumferential and distal resection margins[44].

Huscher *et al*.[43] reported seven cases of TME using a hybrid technique combining robotic TaTME and laparoscopic abdominal procedure (vessel division and colon mobilization). Macroscopic assessment showed complete mesorectum in six cases and near complete mesorectum in one case, the mean number of lymph nodes was 14 and DRM and CRM were negative in all cases[43].

CONCLUSION

TaTME offers several potential advantages compared to standard transabdominal TME. Several trials are currently underway to test this hypothesis. The single port robot may further facilitate introduction and adaptation of the TaTME method of TME.

DECLARATIONS

Author's contribution

Writing manuscript, critical review and final edits: Wexner SD
Writing manuscript and final edits: Yellinek S

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Dr. Wexner is a paid consultant and receives royalties from Intuitive Surgical Karl Storz Endoscopy, and Medtronic and consulting fees from Novodaq.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Mini-invasive Surgery

Case Report

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Endoscopic ultrasound-guided drainage of the biliary tree in malignant obstruction

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) with stenosis stenting is the procedure of choice for treatment of malignant biliary obstruction. It has a low failure rate (< 5%-10% in cases of normal anatomy). The traditional alternative is radiological percutaneous drainage with a variable and non-negligible burden of adverse events. Interventional endoscopic ultrasound offers real-time imaging of the bilio-pancreatic district with the possibility of accessing the main biliary duct and the left hepatic duct from the duodenum or stomach. Consequently, endoscopic ultrasound-guided biliary drainage, including the rendezvous technique, choledochoduodenostomy, and/or hepatico-gastro or antegrade stenting, has become a realistic option that offers advantages of a faster and cost-saving procedure since it can be performed immediately after ERCP, thus avoiding repeated sessions and prolonged hospital stays. We describe a case of malignant obstruction of the common bile duct that was drained by creation of choledocho-duodenal anastomosis under ultrasound-guided endoscopy.

Keywords: Endoscopic ultrasound, biliary drainage, pancreatic cancer, ultrasound-guided biliary drainagex

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) with stenosis stenting is the procedure of choice for treatment of malignant biliary obstruction. Even though it has a low failure rate, < 5%-10% in cases of normal anatomy. ERCP can be unsuccessful in cases of gastric outlet obstruction or unidentifiable papilla such as duodenal stenosis, post-surgical anatomy, duodenal diverticula, and/or tumor infiltration of the papilla. When ERCP fails, the traditional alternative is percutaneous biliary drainage (PTBD), which has significant morbidity and mortality rates compared with ERCP. Major complication rates after PTBD vary between 0.5% and 2.5%. Major complications include bleeding, surgical site infections, cholangitis, bile leaks, pneumothorax, and catheter dislodgement. Procedure-related mortality is < 2% in most series[1].

Endoscopic ultrasound offers real-time imaging of the bilio-pancreatic district with the possibility of guiding complex procedures, including direct access to the main biliary duct and the left hepatic duct from the stomach or duodenum. For these reasons, endoscopic ultrasound-guided biliary drainage (EUS-BD) has been increasingly investigated, and it has been proposed as an alternative to PTBD if ERCP fails. Since Wiersema *et al.*[2] reported the first experience of endosonography-guided cholangiopancreatography, and Giovannini *et al.*[3] described the creation of a choledochoduodenal anastomosis, various EUS-guided procedures for accessing the biliary tree from the duodenum or stomach have been described. Once a biliary duct has been punctured, either the left intrahepatic ducts from the proximal stomach or the main duct from the duodenal bulb, a tract between the biliary tree and visceral lumen is created by a cystotome and a stent is inserted to allow the creation of an anastomosis. Either plastic or, preferably, self-expandable metal stents can be used, the last being fully or partially covered to minimize the risk of bile leakage. More recently, a novel electro-cautery lumen-opposing self-expanding metal stent (Hot AXIOS™ stent and delivery system) that is used to perform EUS-BD (choledocho-duodenal anastomosis) has been developed with the promise to allow faster and safer procedures[4].

EUS-BD appears to be an effective technique for the treatment of biliary obstruction after unsuccessful ERCP. However, it is a complex procedure, requiring endoscopic and ultrasonographic skills in addition to an interventional radiology and surgical support in order to ensure a safe procedure in case of adverse events. We herein report a case of successful EUS-DB in a patient with malignant obstruction of the common bile duct, with special emphasis on the technical aspects of this approach including a video of the procedure.

CASE REPORT

A 71-year-old male patient with biliary obstruction was referred to our department for tissue sampling and endoscopic biliary stenting with the view of further oncological therapy. An abdominal computed tomography (CT) scan showed multiple abdominal adenopathies and pathological tissue involving the hepatic hilum and the pancreatic head with dilation of the main biliary tract and minimal dilation of the intrahepatic biliary tree. After multidisciplinary tumor board evaluation and discussion of the therapeutic options with the patient including the informed consent, he was scheduled for endoscopic drainage. Endoscopy was carried out under deep sedation with midazolam and propofol. During endoscopic exploration, malignant infiltration of the second portion of the duodenum was evidenced, which hindered the procedure after a few ERCP attempts (TJF-240; Olympus Medical Systems, Tokyo, Japan). A stepwise approach was planned during the same endoscopic session. After prophylactic antibiotic therapy was administered (ceftriaxone 2 g), a EUS-guided rendezvous was performed with access from the duodenal bulb to the main biliary tract. A 0.025-inch guidewire (VisiGlide II; Olympus Medical Systems, Tokyo, Japan) was passed across the papilla through a 19G needle (EchoTip® Ultra HD Ultrasound Access Needle, Cook Medical, Limerick, Ireland), up to the duodenum. Wire capture via a snare passed through the duodenoscope was unsuccessful due to the difficult duodenal access, and after a few attempts the guidewire had to be retrieved [Figure 1A and B]. As a second option, EUS-BD from the duodenal bulb was chosen. A linear echoendoscope with a 3.7-mm working channel (GF-UCT180 Linear Ultrasound Endoscope, Olympus Medical Systems, Tokyo, Japan), connected to an ultrasonographic processor (EU ME2, Olympus Medical Systems, Tokyo, Japan) was used to visualize the main biliary tract from the duodenal bulb. Color Doppler ultrasound was used to assess the local vascularization. The common bile duct was punctured with a 19-gauge needle (EchoTip® Ultra HD Ultrasound Access Needle, Cook Medical, Limerick, Ireland). Under fluoroscopic guidance, the bile was aspirated and iodine contrast medium was injected in order to delineate the bili-

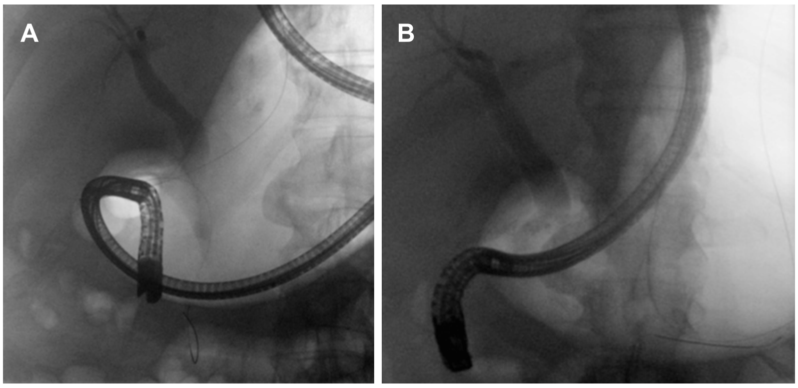

Figure 1. (A) Rendez-vous attempt from the duodenal bulb. The wire was positioned through the papilla, but it could not be retrieved because of the duodenal stenosis. After a few attempts the wire had to be retracted as it can be seen in the stomach (B)

ary tree. A 0.025-inch guidewire was passed through the 19G needle that was positioned in the common bile duct, and the 19-gauge needle was then exchanged with a 6Fr cystotome (Endoflex, Voerde, Germany), which was activated to create a communication between both visceral lumens. A 4-mm biliary dilation balloon (MaxForce™ Biliary Balloon Dilatation Catheter, Boston Scientific, Marlborough, USA) was used to dilate the tract and subsequently a preloaded (delivery catheter: 8.5 Fr/2.83 mm) fully covered 60 mm × 10 mm self-expandable metal stent (Biliary RX Fully Covered Stent System RMV, Boston Scientific, Marlborough, USA) was easily inserted leading to satisfactory drainage. As a further measure to avoid bile leakage and set the metal stent in a stable position, a double pig-tail plastic stent 50 mm × 7 Fr (Advanix™ Biliary Stents, Boston Scientific, Marlborough, USA) was inserted along the conduit between the biliary and gastrointestinal tract [Video 1]. The patient had an uneventful recovery and the jaundice improved rapidly. He received chemotherapy for a high-grade B-cell lymphoma diagnosed on duodenal biopsies. A CT-scan performed one month later confirmed the correct position of both stents [Figure 2].

DISCUSSION

In patients with jaundice due to malignant obstruction, EUS-BD has been studied in recent years as an alternative to PTBD after failed ERCP. In 2001, Giovannini *et al.*[3] were the first to report the creation of a bilioduodenal anastomosis under ultrasonographic guidance in a patient with pancreatic head cancer. Since then, experience has expanded, and various EUS-guided procedures for biliary tract diseases have been reported, including EUS-guided rendezvous choledochoduodenostomy, hepaticogastrostomy, and antegrade stent insertion[5-10]. Nowadays, ERCP and EUS-BD have similar success and complication rates in experienced hands, with a lower post-procedural pancreatitis rate after EUS-BD. Furthermore, recent studies have shown that EUS-BD is associated with better clinical success rates, lower adverse events rates, and fewer reinterventions than PTBD[11]. A study by Dhir *et al.*[7] showed an average incidence of bile leaks of 3.9% in 432 patients; where most of the leaks were mild. Serious complications, such as stent migrations in the peritoneal cavity, sepsis, and perforations have rarely been described. Data on long-term stent patency are scant, but do not seem to differ significantly to that of ERCP stenting[7].

With regards to the access route, transgastric and transduodenal endoscopic approaches have similar success rates and complications, of more than 90% and around 20% respectively[12-16]. As a matter of fact, the access route is often determined more by the endoscopist's expertise or preference than by evidence-based indications. The transhepatic route through the stomach offers the advantage of a reduced bile leakage risk although the scope position is less stable, whereas the transduodenal route appears easier to manage because of direct access to the main biliary duct. In 2016, Tyberg *et al.*[17] proposed an interesting approach to biliary drainage based on the anatomical condition of the patient as defined on cross-sectional

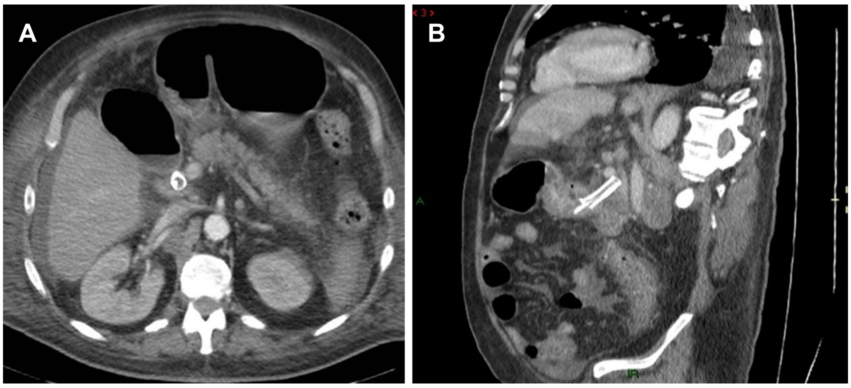

Figure 2. Control CT-scan on (A) axial plane and (B) sagittal reconstruction showing both plastic and metal stents in place

imaging. The authors defined an algorithm based on anatomy more than on the endoscopist's preference, so it required good technical experience with respect to different drainage procedures, which could also be applied in a sequential manner. Notably, they reported a high technical success rate (96%) with a low rate of adverse events (10%). In accordance with Tyberg's alghorithm, the first element to be evaluated is intrahepatic bile ducts dilation. If dilation is noted, anterograde stenting or hepatico-gastric drainage are suggested. If intrahpeatic ducts are not dilated, a rendezvous-based technique (from the intrahepatic or extrahepatic tract) is suggested. If this fails, transenteric stenting is still feasible. This interesting algorithm standardizes the EUS-BD approach for patients with biliary obstruction.

EUS-BD offers some clear advantages over ERCP. First, it does not require papillary cannulation, which carries out a risk of post-ERCP pancreatitis. Second, it allows creation of an anastomosis at a distance from the tumor, thus avoiding the risk of ingrowth or overgrowth with consequent stent dysfunction. Furthermore, EUS-BD can target different sites of the biliary tree, thus allowing drainage also in unfavorable situations both for ERCP, such as gastric outlet obstruction or post-surgical anatomy, and for PTBD such as ascites or liver lesions[18]. In comparison with PTBD, EUS-BD appears to be faster and more cost-saving, since the procedure can be performed immediately after ERCP, thus avoiding repeated procedures and prolonged hospital stays[19-21]. On the other hand, performing this type of biliary recanalization may hamper endobiliary ablation, a technique used to control endobiliary tumor growth, and this may be a disadvantage of the EUS-BD technique. However, trans-luminal EUS-guided radiofrequency ablation by specifically designed active needles (such as EUSRA™ RF Electrode-VIVA RF Generator, STARmed, Seoul, Korea or Habib™ EUS-RFA catheter, Emcision Ltd., London, UK) is feasible and probably facilitated by the absence of a standard biliary stent in the tract involved by a pancreatic tumor[22,23].

In conclusion, even though we are still far from routine use of EUS-BD in common practice, it has been shown as a feasible and promising alternative to PTBD after failed ERCP. More emphasis on routine use of these procedures will come from recent development of dedicated accessories in addition to diffusion among endoscopists of the knowledge and practice of advanced ultrasonographic procedures.

DECLARATIONS

Author's contributions

Performed the procedure: Armellini E, Ballarè M
Drafted the paper: Armellini E
Edited the movie clip: Mazza F, Donato G
Revised the manuscript for relevant intellectual content: Orsello M, Occhipinti P

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Conflicts of interest
The author declares that there are no conflicts of interest.

Ethical approval and consent to participate
Ethical Board approval was not required.

Consent for publication
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Mini-invasive Surgery

Review

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Is laparoscopic rectal surgery really not non-inferior?

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Abstract
Laparoscopic rectal surgery has gained popularity over the last 20 years. Currently there are still questions surrounding the safety and efficacy of this technique as compared to the traditional open modalities. To date, despite the initial enthusiasm for laparoscopic rectal surgery this technique is yet to reach non-inferiority in trials when compared to open resection. This review article discusses the current evidence exploring the value of laparoscopic rectal surgery. It will discuss its evolution over the last 20 years, exploring all the major randomised control trials and their results. It is our belief that laparoscopic rectal surgery for malignancy is not non-inferior to conventional open surgery.

Keywords: Rectal cancer, laparoscopic, open surgery, non-inferior, survival rate

INTRODUCTION
In Western society, rectal cancer is the third most common cause of cancer related deaths[1]. It encompasses approximately 30% of all colorectal malignancies[2]. Surgical resection of the rectum remains pivotal to the successful management of rectal cancer, especially in stage II or III disease[3,4].

The treatment of rectal cancer has undergone significant change over the last 50 years. Prior to total mesorectal excision (TME) rectal cancer had a locoregional recurrence rate of 40% and 5-year survival of less than 50%[5,6]. It was revolutionised in the early 1980's by Heald, who demonstrated that TME significantly improved the outcomes and prognosis for patients being treated for rectal cancer[6]. TME is the precise surgical dissection technique which involves the complete removal of the rectum, together with its draining lymph nodes, within an intact mesorectum[1]. TME, in addition to neoadjuvant and adjuvant treatments have led to a reduction in locoregional recurrence to less than 10% and 5-year survivals of more than 70%[7,8]. The removal of the rectum and its mesorectum allows for potentially curative resection, pathological staging, prognosis and aids in further treatment decisions[9]. The quality of this resection is associated with improved outcomes in terms of survival and locoregional recurrence, thus the push for standardised good quality surgery[10,11].

Over the last 30 years there has been a drive towards minimally invasive techniques. Advances in laparoscopic surgery was thought to further revolutionise the surgical treatment of rectal cancer. Current evidence supports the concept of laparoscopic colonic resection over the traditional open modalities with known improvements in short-term outcomes, in addition to equivalent long-term results, when compared to open surgery[12,13]. In the short-term patients were noted to have faster recoveries, earlier feeding, decreased overall morbidity, earlier return of bowel function and decreased amounts of intraoperative blood loss[14,15]. In the intermediate term there was an earlier return to work. More importantly though the long term oncological outcomes regarding local recurrence, disease free survival and overall survival were shown to be improved[16].

Unfortunately to date the promise of similar results in laparoscopic rectal surgery has not yet been delivered. Several studies have shown laparoscopic rectal surgery has failed to reach noninferiority when compared to open resection in terms of short term pathological outcomes[10,17]. However, early reports from some of the major trials are suggesting that laparoscopic rectal surgery and open resection are equivalent regarding long-term disease-free survival, overall survival and local recurrence[18-20].

This review article aims to answer the question "is laparoscopic rectal surgery really is non-inferior to open surgery?" Is there too much focus on the short term pathological outcomes or should we be more patient and wait for the long-term survival data before we answer this question?

This article will outline the evidence to date, discuss the evolution of laparoscopic colonic surgery and its applicability to rectal surgery and finally discuss the current evidence for long term oncological outcomes and the evidence that is yet to be published. It is our belief that laparoscopic rectal surgery is not non-inferior to open surgical techniques in experienced hands.

EVOLUTION OF LAPAROSCOPIC COLONIC SURGERY

Laparoscopic colonic surgery had a relatively slow progression into accepted surgical practise. It was noted to have a steep learning curve, there was limited evidence regarding randomised control trials (RCTs), concerns were raised regarding its lymph node harvests, oncological outcomes and reports of port site metastasis[21]. Eventually over time, these concerns were laid to rest with robust, quality evidence. Laparoscopic colectomies have proven to be not only cost effective but have shown to have improved short-term outcomes with equivalent long-term oncological outcomes[21].

In 1991, Jacobs *et al.*[22] published their first case series of 20 patients who had received laparoscopic assisted colectomies. Lacy[23] published the first RCT which was a single institution study comparing 219 patients. This study revealed significant short-term benefits for the laparoscopic patient group regarding reduced blood loss, early return of intestinal function and overall decreased morbidity[23]. However, concerns were raised over the low lymph node harvests in both groups (average yield of 13 lymph nodes) and the low number of patients receiving adjuvant chemotherapy[21,23]. Furthermore, there were initial concerns raised about port site metastasises with reported incidences of 1%-21%[24]. Ultimately this was disproven, with an accepted incidence of 1%[19]. The accepted incidence of cutaneous metastasis after open resection is 1%-1.5%[25].

Eventually large randomised trials such as COST (Clinical Outcomes of Surgical Therapy) Study group, COLOR (Colon cancer Laparoscopic or Open Resection) trial, ALCCaS (Australian laparoscopic colon cancer study) trial, and the MRC CLASICC (Conventional versus laparoscopic-assisted surgery in patients with colorectal cancer) have shown the safety and efficacy of laparoscopic colonic surgery[26-28]. This same journey seems to parallel that of for laparoscopic rectal surgery. Currently the main criticism is that the short term oncological outcome of the resected specimen is not reaching noninferiority of the same specimens resected via open surgery. However, the long-term survival data that is emerging, is supporting equivalent outcomes regarding long term disease free survival, overall survival and locoregional recurrence.

COMPLEXITIES OF LAPAROSCOPIC RECTAL SURGERY

Laparoscopic rectal surgery can be divided into an abdominal component and a pelvic component. For the operation to be considered laparoscopic both components need to be completed laparoscopically. Regarding the traditional open operations this could be achieved by either the conventional laparotomy or via a hybrid procedure where the abdominal component is accomplished by laparoscopy (therefore taking advantage of the known benefits of laparoscopic colonic surgery). The pelvic component is then completed via a pfannensteil incision which allows direct vision of the rectum and surrounding mesorectal envelope[17,29].

There are several theoretical advantages to completing the operation completely laparoscopically as compared to open. The first of which is an intensely magnified view of the pelvis, which could allow improved preservation of the autonomic nerves. Furthermore, this magnification could lead to better visualisation of the TME plane and theoretically allow a more precise dissection. In addition to this, there has been evidence to support less blood loss, earlier feeding, early return of bowel function and decreased length of stay in hospital following laparoscopic procedures[29].

However, the learning curve of laparoscopic TME dissection is significant and requires time to master; more so than that of the curve for laparoscopic colonic resections. It is particularly challenging working within the narrow, confined space of the bony pelvis which creates issues with tissue retraction and dissection of the mesorectum[29]. Furthermore, the technical issues with laparoscopic equipment, particularly with laparoscopic stapling devices and the linear energy devices can be quite difficult to use inside the rigid, narrow pelvis, therefore requiring a high level of surgical expertise[29].

EVIDENCE FROM MULTICENTRE RANDOMISED CONTROL TRIALS (SHORT TERM ONCOLOGICAL DATA)

To date there have been several studies comparing the short term oncological outcomes of laparoscopic rectal surgery to that of open surgery. The landmark multicentre RCTs include the early UK-based MRC CLASICC (Conventional *vs.* Laparoscopic-Assisted Surgery in Colorectal Cancer) trial[27], the North American COLOR (Colon Cancer Laparoscopic or Open Resection) II trial[18], the South Korean based COREAN (Comparison of Open Versus Laparoscopic Surgery for mid or low Rectal Cancer After Neoadjuvant Chemoradiotherapy) trial[20], the Australian based ALaCaRT (Australian Laparoscopic Cancer of the Rectum Trial) trial[17] and the US based ACOSOG Z6051[10].

Some of the earliest data published came from the MRC CLASICC trial which was published in the Lancet in 2005. This was a multicentre trial that compared laparoscopic colon and rectal surgery to the conventional open modalities. Overall, the trial recruited 794 patients of which 242 had rectal cancer between 1996 and 2002. The relatively concerning results reported, likely reflected the challenges of laparoscopic rectal surgery and its early utilization. Thirty-four percent of patients required conversion, there was a 5% mortality rate and there was a high positive circumferential resection margin (CRM) rate of 12% for the laparoscopic group and 6% for the open group. As compared to the 2015 ALaCaRT trial which had a 6.7% positive CRM rate in the laparoscopic group[27].

COLOR II trial was a noninferiority trial that recruited 1044 patients from 30 centres across 8 countries between 2004 and 2010, with adenocarcinoma of the rectum, within 15 cm of the anal verge. The primary outcome measure was to compare the locoregional recurrence after 3 years. Secondary outcome measures was 3-year disease free and overall survival. Included in the analysis was a comparison of the pathological data of the resected rectums. On pathological analysis the authors did not find any significant difference in TME quality, CRM or distal resection margin (DRM)[18].

The COREAN trial recruited 340 (170 patients in each group) patients with mid to low rectal cancer from 3 tertiary hospitals in South Korea between 2006 and 2009. It differs from the other trials in that all their patients received neoadjuvant chemoradiotherapy, whereas not all patients received neoadjuvant treatment in ALaCaRT or ACOSOG Z6051. Short term outcome measures such as CRM, TME quality, DRM and number of harvested lymph nodes were collected. Other measures such as post-operative quality of life, morbidity and return of bowel function were also investigated. Secondary outcomes included longer term outcomes (disease free and overall survival) at 3 years. Pathological assessment of the resected specimen in this study showed no statistical difference between the groups. The authors in this study supported the use laparoscopic rectal surgery after neoadjuvant chemoradiotherapy as it had an improved short-term benefit regarding post-operative outcomes and its pathological assessment was equivalent between the two groups[20].

ALaCaRT was a multicentre, randomised, noninferiority trial which aimed to investigate the safety and outcomes of laparoscopic rectal surgery as compared to open surgery. It recruited 475 patients (237 open resection group and 238 laparoscopic resection group) from 24 institutions from across Australia and New Zealand between 2010 and 2014 with T1-T3 rectal cancers within 15 cm of the anal verge. The primary aim of the study was to compare pathological outcome of the resected specimen. Secondary outcome measures compared were disease free survival, local pelvic recurrence at 2 years and overall survival at 5 years. The oncological quality of the specimen was a composite measure of completeness of TME, CRM and DRM. A successful resection needed to fulfil all the requirements of the composite outcome. The major distinction of this trial compared to the other landmark trials was the incorporation of the hybrid technique into the open group. The results failed to show that laparoscopic rectal surgery is non-inferior to open rectal surgery with only 82% of laparoscopic resected specimens being considered successful in contrast to 89% of the open group. However, the quality of the surgery was high, with 87% of laparoscopic TME's being complete, 93% of CRM negative and a clear DRM in 99%. The conversion from laparoscopic to open was only 9%. The authors concluded that there wasn't sufficient evidence for the routine incorporation of laparoscopic rectal surgery. The longer-term outcome measures are still awaited[17].

ACOSOG Z6051 was a similar study to ALaCaRT as it also evaluated the short term pathological outcomes using the composite outcome measures defined previously. It was a multicentre, randomised control trial that recruited 462 patients with clinical stage II or III rectal cancer (laparoscopic resection n = 240, open resection n = 222) from 35 institutions across the United States and Canada between October 2008 to September 2013. The only difference is that the ACOSOG Z6051 defined an acceptable TME as either complete or nearly complete (TME Grades 2 and 3) whereas the ALaCaRT trial only considered a complete TME (TME Grade 3) as successful. As with the ALaCaRT trial this multicentre trial failed to prove that laparoscopic rectal cancer was non-inferior to open rectal surgery. The results revealed 81.7% of laparoscopically resected specimens as compared to 86.9% of the open group were successful resections with respect to the composite pathological outcome measure. The conversion rate was only 11.3% which suggested the quality of surgical experience was high. The authors concluded that their findings did not support the use laparoscopic rectal resection[10].

The evidence from these landmark trials has highlighted the improvement in oncological outcomes as experience and expertise with laparoscopic rectal surgery increases.

LONGER TERM ONCOLOGICAL OUTCOMES FOR RECTAL SURGERY

At present, there is only limited published data available for the longer term oncological data that compares laparoscopic and open approaches to rectal cancer. Currently, available datasets include the 10-year data from the MRC CLASICC trial, the 3-year data from the COREAN and COLOR II trials. The initial 2-year longer term oncological outcomes are still awaited from ALaCaRT and ACOSOG Z6051 trials.

The MRC CLASICC trial has revealed quite promising outcomes in terms of locoregional recurrence, disease free survival and overall survival after 10 years. There was no difference in the overall survival, disease free survival or local recurrence on subgroup analysis. The median disease-free survival was 70.6 months (open 67.1 months, laparoscopic 70.8 months; $P = 0.925$) with the median overall survival being 73.6 months (65.8 months open group, 82.7 months laparoscopic group; $P = 0.147$)[19].

In the COREAN trial the 3-year disease free survival was 79.2% for laparoscopic surgery and 72.5% for the open resection group[20], which was not statistically significant. There was also no significant difference in the rates of local recurrence or overall survival (disease free survival $P = 0.34$). These results were similar to the results of the COLOR II trial in which 3-year disease free survival was 74.8% in the laparoscopic surgery group and 70.8% in the open group, which did not result in a statistically significant difference[18]. The 3-year overall survival of the laparoscopic and open TME groups was 86.7% and 83.6% respectively. This was not statistically significant. Both groups in the COLOR II trial had a 5% locoregional recurrence rate[18]. In both studies, the authors concluded that laparoscopic rectal surgery was comparable to that of the open resection group.

EVIDENCE FROM META-ANALYSES FOR RECTAL CANCER

The most recent meta-analysis was published by Arezzo *et al.*[30] in 2015. This included all RCTs and non-randomised control trials published between 2000 and 2013 (therefore not including the ALaCaRT and ACOSOG Z6051 trials). Their ultimate primary end point was CRM positivity, but they also analysed DRM, quality of TME and local recurrence at 5 years. Essentially this revealed no significant difference in any of these outcome measures. The authors concluded that there was some evidence to support laparoscopic rectal resection in terms of short term outcomes, pathological outcomes and longer-term outcomes[30].

Moreover, there was a Cochrane review article published in 2014 that evaluated the short and longer-term outcomes of laparoscopic and open rectal surgery. This review only reviewed RCTs. The conclusion was that there was moderate strength evidence to support laparoscopic resection. It revealed similar outcomes for disease free survival, overall survival and local recurrence. In addition, it also noted that there was a decrease in hospital length of stay and time to first defection in the laparoscopic resection group[1].

Even though the evidence is not considered to be as strong, the general impression is that laparoscopic rectal surgery is not non-inferior to open rectal resection.

SHIFTING OF FOCUS

Should the focus of these noninferiority studies shift focus from immediate oncologic analysis and focus more upon the long-term survival data? In an experienced surgeon's hands there appears to be a definite short-term benefit regarding reduced post-operative morbidity and hospital length of stay[29]. This cannot be accepted if the long-term survival data is not equivalent to that of the open surgical group.

Of note, there is overwhelming data supporting that there are improved outcomes with the increasing quality of TME excision. However, this evidence was collected in the open operation era. Is quality of the TME the only predictor in overall survival? Bouvy *et al.*[31] published an article in 1997 which suggested that laparoscopic surgery was associated with less tumour growth when compared to conventional open surgery because of the reduced operative trauma. They believed that reduced operative stress lead to decreased production of growth factors and therefore decreased stimulation of tumour cell growth[31]. More recently, endocrine and metabolic markers have been studied in attempt to quantify this operative stress. Human leukocyte antigen (HLA) and the pro-inflammatory marker interleukin 6 (IL-6) have been proposed potential surrogates to measure the surgical stress response. The evidence suggests that there is preserved immune function and less inflammation in laparoscopy as compared to the conventional open resections[32].

Could this be the reason that despite current trials being unable to show non-inferiority, early survival data appears equivalent? To answer this, we await the survival data from the more recent trials with great interest.

Should the next focus be more on the quality of the TME using minimally invasive techniques (robotics or trans-anal TME)? If we are currently obtaining equivalence in survival outcomes with lower grade TME quality, surely survival will improve with the development of higher quality minimally invasive TME.

Kim *et al.*[33] have recently published their experience with robotic TME. They retrospectively compared 732 patients (robotic n = 272; laparoscopic n = 460) aiming to evaluate the long term oncological outcomes between the robotic and laparoscopic TME. Ultimately, they were able to show that the overall 5-year survival for robotic TME and laparoscopic TME was 90.5% and 78% respectively, with the 5-year disease free survival being 72.6% and 68% respectively. Despite the limitations of this study, it does reveal that robotic TME may have a meaningful impact on long term outcomes (in regard to overall survival and disease free survival)[33]. Long-term oncological outcomes from the prospective trials Robotic versus Laparoscopic Resection for Rectal Cancer (ROLARR) and Comparison of Laparoscopic versus Robotic-Assisted Surgery for Rectal Cancer (COLRAR) trials are awaited.

CONCLUSION

Currently there is conflicting evidence for the role of laparoscopic TME for rectal cancer patients. The evidence from recent well executed RCTs would suggest that the short term oncological outcome of the laparoscopic TME has failed to reach noninferiority. The long-term survival data from the limited literature is promising and is showing equivalence between the 2 groups. However more evidence from recent trials needs to publish to further evaluate this.

It is our belief that in experienced hands laparoscopic rectal resection is not non-inferior but is equivalent to open resection. In saying this, it is important that whichever modality is chosen, that the surgeon is comfortable and well trained in that technique. Ultimately the quality of the surgery will facilitate the outcomes for the patient and hopefully the desired long-term outcome.

DECLARATIONS

Authors' contributions

Design, manuscript editing, manuscript revision: O'Donohue PF, Warren CD, Chow CFK
Literature research, data analysis, manuscript writing: O'Donohue PF, Warren CD

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Mini-invasive Surgery

Review

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Completion proctectomy following transanal endoscopic microsurgery for early rectal cancer

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Abstract
Transanal endoscopic microsurgery (TEM) has proven to be a safe and effective procedure in removal of rectal lesions and may be used in treatment of early rectal cancer in selected patients. In cases when the TEM specimen shows non-radical resection, or histological high-risk factors, completion proctectomy (CP) is warranted. It is debated when it is the best time to perform CP following TEM. It is furthermore uncertain whether CP leads to an increased risk of abdominoperineal excision. Herein, we review the available literature regarding controversial issues with early completion proctectomy following TEM.

Keywords: Transanal endoscopic microsurgery, total mesorectal excision, completion proctectomy, early rectal cancer

INTRODUCTION
Transanal endoscopic microsurgery (TEM) was first introduced in 1984 by Buess *et al.*[1] as a minimally invasive surgical technique for the resection of large rectal adenomas. With TEM technique, a full-thickness *en bloc* excision is possible in the entire rectum, which may be technically difficult by other local procedures such as transanal excision (TAE). TEM has proven to be a safe and effective procedure in removal of rectal lesions[2-9]. TEM has furthermore considerably lower morbidity and mortality compared with conventional radical rectal resection for rectal tumors[10-15]. For patients with tumors in the lower part of the rectum, local excision by TEM may offer a chance for preserved bowel continuity and avoidance of rectal amputation with subsequent consequences.

The best management for early rectal cancer is still controversial. In terms of oncological results, local excision of early rectal cancer (pT1) by TEM has equivalent outcomes to radical resection[10,11,13,14]. Due to abovementioned advantageous attributes, the use of TEM for early rectal cancer is now considered a viable option in selected patients, and may be offered to patents with lesions pre-operatively staged as T1N0, with tumor diameter < 4 cm involving less than 30% of the rectal wall circumference, and no histological risk factors[16-20]. Preoperative staging with endoscopic rectal ultrasound (ERUS) and magnetic resonance imaging (MRI) of rectal lesions aid in decision making of selection for local treatment or radical resection. However, understaging is not uncommon[9,21-25]. Furthermore, unexpected malignancy is reported in 18%-43% of preoperatively assumed benign lesions in the rectum[9,26-28].

Early completion proctectomy (CP) is recommended in cases when the TEM specimen shows non-radical resection, low tumor differentiation or lymphovascular invasion, because of the increased risk of recurrence and lymph node metastasis in such cases. Some concerns have been raised regarding early CP. There may be increased morbidity due to two procedures being performed in the same area within a short period of time. The healing and scar formation and mesorectal fibrosis from the previous TEM procedure may disrupt the normal tissue planes and compromise the operative field. This may increase the difficulty during dissection in CP, and result in higher perforation rates, poor resection quality, prolonged operative time and higher conversion rates. The fibrotic scarring following TEM procedure may also contribute to tissue retraction and binding of the previous tumor site to the pelvic floor, which may lead to an increased abdominoperineal excision (APE) rate. We aim to review the available literature regarding controversial issues with early completion proctectomy following TEM.

OVERALL MORBIDITY AND APE RATE

Overall morbidity following rectal cancer surgery is about 40%, regardless of approach (open or laparoscopic)[29]. A concern with CP is that a previous operation in the rectum by TEM may influence surgical dissection plans, resulting in an increased risk for local complications. Regarding morbidity rates following CP, the results vary among studies, and interpretation is limited by small study samples and methodological issues. In a study reported by Piessen *et al.*[30], 14 consecutive patients who underwent full thickness TAE and subsequent radical resection, were matched and compared with 25 patients with primary radical resection. There was no significant difference in overall morbidity (64.3% *vs.* 32%, P = 0.112). However, a higher rate of surgical complications was shown in the TAE group (57.1% *vs.* 20%, P = 0.048). The frequency of specific surgical site complications, including anastomotic leakage and pelvic abscess, was also higher in the TAE group (42.8% *vs.* 8%, P = 0.032). The study cohort consisted of patients with preoperative chemo- or radiation therapy (5/14 patients in the TAE group), and the defect in the rectal wall was left unsutured in all patients, which may have contributed to the higher local compliactions. Although not fully investigated yet, the non-sutured defect at the TEM site may weaken the rectal wall and result in higher risk of perforation during CP.

In contrast, Morino *et al.*[31] didn't find any difference in the incidence of complications. They compared 17 patients with laparoscopic total mesorectal excision (LTME) after TEM with 34 patients undergoing primary TME and found that the results on rate of intraoperative complications and conversion to open surgery did not differ significantly (5.9% *vs.* 8.8%, P = 0.854, and 5.9% *vs.* 5.9%, P = 0.528, respectively). There was, however, a significantly longer operating time in the TEM group (206 min *vs.* 188 min, P = 0.025). Although there were only 25 patients in each group, the study by Levic *et al.*[32] is the largest comparative study on early CP up to date. Twenty-five patients with early CP were matched and compared with 25 patients with primary TME. There was no difference in intra- or postoperative complications, operating time or estimated blood loss between the two groups. Only a minority of the patients in both groups were operated with laparoscopy, hence it is therefore not possible to say whether previous TEM had an influence on conversion rates.

The fibrotic changes in the mesorectum and granulation tissue surrounding the previous TEM site is also a concern following CP, because of potentially higher APE rates. Although recognized among surgeons, there is still a lack of evidence on the subject in the literature. Hompes *et al.*[33] reported a 14% APE rate in a study consisting of 36 patients with CP. Piessen *et al.*[30] didn't find any difference in rate of sphincter saving procedures performed. One of the matching factors was, however, the procedure type. Likewise, there was no difference in the APE rate in the study by Levic *et al.*[32], although the control group was also matched based on procedure type. Morino *et al.*[31] performed matching based on gender, age, American Society of Anesthesiologist (ASA) score, body mass index (BMI), tumor size, and tumor distance from the anal verge. A significantly higher APE rate was observed in the CP group (41.2% *vs.* 11.7%, $P = 0.028$). Following multivariate analysis, previous TEM was the only independent predictor for APE (OR 4.13, 95%CI 1.09-15.55, $P = 0.046$)[31]. In a study by van Gijn *et al.*[34] where 59 patients with CP were compared with 881 patients from the TME-trial (with preoperative radiotherapy) the results showed a higher rate of colostomies in patients with previous TEM (OR 2.51, 95%CI 1.30-4.86, $P = 0.006$). The TEM group had, however, a higher rate of Hartmann procedures, but the same rate of APE.

PATHOLOGICAL FINDINGS

Another concern with CP after TEM may be pathologic findings and completeness of the mesorectal fascia (MRF). The risk of poorer quality of the mesorectum may be due to the scar formation and mesorectal fibrosis from the previous TEM, as previously mentioned. In Morino's study, where a higher rate of APE was reported, no difference was seen in the integrity of the mesorectum, with preserved integrity in all patients included in the study[31]. Likewise, although there were incomplete pathological data on all patients, Levic *et al.*[32] didn't find any difference in the number of patients with nearly complete or complete MRF (11 *vs.* 16 patients, $P = 0.31$). The perforation rate at or near the previous TEM site was, however, 20% in the CP group. Piessen *et al.*[30] reported major difference in completeness of the mesorectum. The MRF was complete in only 4/25 with previous full-thickness TAE *vs.* 24/25 in the group with primary TME ($P < 0.001$). Furthermore, tearing of the rectal wall down to the mucosa occurred was more frequent in the group with CP (35.7% *vs.* 0%, $P = 0.009$). Again, it is worth to mention that the defect after the full thickness excision was left unsutured in all patients, which may have had an influence on these figures. None of the studies comparing CP with primary TME showed difference in the circumferential margin involvement rate (Levic *et al.*[32]: 4% in both groups; Morino *et al.*[31]: 0% in both groups; Piessen *et al.*[30]: 14% *vs.* 4%).

ONCOLOGICAL RESULTS

The reported high perforation rates during CP lead to worries regarding survival in these patients, as iatrogenic rectal perforation is one of the most important risk factors for both local and distant recurrence and impaired survival[35-37]. Results regarding long-term oncological results in patients with CP are, however, very limited. Borschitz *et al.*[38]'s study on 21 patients with CP following TEM showed low rates of both local recurrence and distant metastases (6%). The 5-year disease-free survival (DFS) was 75% in patients with T1R0, and 93% in patients with T1/R1 or those with "high risk factors". Similarly, Hompes *et al.*[33] reported good survival rates with 1-year DFS of 91% and 5-year DFS of 83%. Local recurrence occurred in 3% (1/36) and distant metastases in 14% (5/36). However, only one study comparing CP with primary TME has reported oncological results[32]. There was no difference in rate of local recurrence between CP and primary TME (0% *vs.* 8%, $P = 0.49$), or rate of distant metastases (4% *vs.* 12%, $P = 0.26$). Cumulative survival rates were not reported. The median follow-up time was 25 and 19 months, respectively. The remaining two studies comparing CP with primary TME only reported short-term results, and oncological data is therefore unfortunately lacking from these studies[30,31].

WHEN TO PERFORM EARLY COMPLETION SURGERY

Whether the time between TEM and CP as an influence on outcomes is not known. The precise definition of "early" and the time frame in which CP should be performed is unclear. Most studies report outcomes after CP perform surgery within 6-8 weeks of TEM. Levic *et al.*[32] defined "early" as CP within 12 weeks of TEM. The median time to CP was 37 days with a range between 14 and 90 days. Similarly, Issa *et al.*[39] had a median time of 47 days to CP (range 32-70) and Piessen *et al.*[30] 37 days (range 7-120). van Gijn *et al.*[34] reported longer interval of 15 weeks to the completion of TME, due to logistic reasons, but the decision of CP was made immediately after the TEM results. In Morino's study only patients with laparoscopic TME within 8 weeks of TEM were included, with a median of 40 days[31]. Hahnloser *et al.*[40] had even shorter criteria, and performed CP following TAE within 30 days, with median time of 7 days. So far only a few studies have reported outcomes based on the time frame to CP. Hompes *et al.*[33] found that poor quality specimen was more frequent after an interval from TEM to CP of more than 7 weeks. The median time to CP was 2 months with range between 0.5 to 8.7 months. However, Morino *et al.*[31] didn't find any difference in outcomes among patients operated within 30 days of TEM or more than 30 days after TEM.

FUTURE ASPECTS

Minimal invasive surgery has gained an increasing interest, especially in the field of rectal surgery. The transanal approach of rectal dissection is gaining wider use and acceptance, and the first randomized trial comparing taTME with laparoscopic TME is currently ongoing[41]. The advantages of trans-anal TME (taTME) include better visualization and possibility of approaching the lesion from below. This may have benefits for patients in need for CP following TEM. Approaching the lesion from below may limit the traction on the scarred tissue and thereby possibly reducing the risk of perforation and other surgical site complications. So far, only one study has reported outcomes of patients with CP by taTME. Letarte *et al.*[42] reported results on 41 patients with CP following TEM, of which 11 were operated by taTME and 30 with conventional TME. The patients with taTME had significantly less intraoperative blood loss (205 mL *vs.* 365 mL, $P = 0.04$). More interestingly, there was lower rate of conversion to open surgery (9.1% *vs.* 57%, $P < 0.001$) and higher sphincter preserving rates (100% *vs.* 50%, $P = 0.01$) despite of the significantly lower distance of tumor from the anal verge in the taTME group.

CONCLUSION

Completion proctectomy following TEM appears safe. Nevertheless, there seems to be an increased risk for intraoperative rectal perforation, which the operating surgeon needs to be aware of. The possible higher incidence of APE following TEM needs to be investigated in larger studies. The drawback in the current literature is the small series reporting outcome of CP following TEM. The published studies on the subject have different methodological approaches, and limited number of patients, which increases the risk of type II error. In order to further investigate whether there is a higher risk of APE and morbidity (particularly rectal perforation, which may influence survival) it is necessary to conduct more studies with higher number of patients, especially those comparing CP with primary TME.

DECLARATIONS

Authors' contributions

Substantial contribution to conception and design, and acquisition of data, and analysis and interpretation of data: Levic-Souzani K, Bulut O

Drafting the article and revising it critically for important intellectual content: Levic-Souzani K, Bulut O

Giving the final approval of the version to be submitted and any revised version: Levic-Souzani K, Bulut O

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Mini-invasive Surgery

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Repeat thermal ablation for local progression of lung tumours: how safe and efficacious is it?

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Abstract

Aim: To retrospectively evaluate the safety and efficacy of repeat thermal ablation for local progression of lung tumours after prior ablation(s).

Methods: From December 2009 to March 2017, 13 patients underwent repeat ablation [11 repeat microwave ablations and 2 repeat radiofrequency ablations] of a lung tumour [9 non-small cell lung carcinomas, 3 metastatic colorectal adenocarcinomas, 1 metastatic pelvic sarcoma] for local progression after prior ablation(s). Safety of the procedure was assessed by presence or absence of adverse events. Efficacy of the procedure was assessed by local tumour response to ablation and survival time.

Results: Repeat ablation procedures were safe, without major adverse events. Median length of hospital stay was 2 days (interquartile range 1-2). Pneumothorax was the most common complication [5 (38%) of 13 repeat ablation procedures]. There was one death within 30 days of ablation, but the cause of death and its relation to the procedure were unknown. Of the 12 patients with imaging follow-up [median follow-up 26 months (range 3-62)], 10 (83%) had complete ablation and 2 (17%) had local progression. Of all 13 patients, 8 (62%) were alive and 5 (38%) had died with a median overall survival of 43 months (95% confidence interval 36-49 months).

Conclusion: Repeat ablation in locally progressing tumours after prior ablation attempt(s) is a safe therapeutic option and often achieves local tumour control.

Keywords: Local progression, lung tumours, microwave ablation, radiofrequency ablation, repeat ablation

INTRODUCTION

CT-guided thermal ablation has developed in the last 20 years as a minimally invasive management option for pulmonary malignancies, both primary and secondary, in patients who are non-surgical candidates[1]. Radiofrequency ablation (RFA), an electric current-based heating technique, has been the most evaluated method[2]. Microwave ablation (MWA), which uses an electromagnetic field around the ablation device to create heat, is a more updated technique with theoretical advantages in terms of lesser susceptibility to heat-sink effect, larger ablations, more uniform ablation zones, and shorter procedural times[2,3]. Ablation failure and subsequent local tumour progression remain an issue for both methods, with tumour diameter greater than 3 cm, proximity to a large vessel and insufficient ablative margin being risk factors for failure[2,4]. There are limited data on the role of repeat ablation for local progression of lung tumours after prior ablation, and with most data on repeat RFA[5-7]. This retrospective cross-sectional study aimed to evaluate the safety and efficacy of repeat MWA and RFA, in locally progressing lung tumours after prior ablation(s) at a large tertiary hospital.

METHODS

Patients

Ethics approval for this study was obtained from the Hospital Institutional Review Board (HREC/14/QRBW/553). Patients were identified using the radiology thermal ablation database at our large tertiary hospital. Data were collected retrospectively through systematic review of patient charts and imaging. Inclusion criteria were consecutive patients who underwent repeat percutaneous CT-guided thermal ablation of a lung tumour for local progression after prior ablation(s) between December 2009 and March 2017. There were no exclusion criteria for this study. Repeat ablation was defined as the most recent ablation procedure, after prior ablation(s). All lesions were referred for ablation if patients are medically inoperable or refuse surgery. Patients were informed of the risks and benefits of ablation, and all provided written informed consent for the procedure.

Ablation procedure and imaging follow-up

Ablations were performed percutaneously under CT guidance (Philips Brilliance 64, Eindhoven, The Netherlands, replaced in 2015 by Aquilion ONE, Toshiba Medical Systems, Otawara, Tochigi, Japan). Both RFA and MWA modalities were used (with MWA having replaced RFA at our institution by mid-2010). All ablations were performed by the same interventional radiologist who had more than 15 years' experience in image-guided ablation. No prophylactic antibiotic treatment was administered. The ablation applicator was inserted under sterile conditions under CT guidance, with analgesia and sedation administered by the anaesthetic team. Parameters such as the type of applicator, number of overlapping ablations, ablation duration, and amount of energy delivered were based on individual tumour size, location and tumour characteristics. Patients received a chest X-ray 3 h post-procedure to assess for post-procedural complications, and in all MWA cases, a limited non-contrast CT scan of the ablated site was performed 24 h post-procedure. Technically successful ablation was defined as completed planned ablation cycle(s) and circumferential perilesional ground-glass opacity. Patients were requested to have serial repeat CT scanning at 3, 6 and 12 months post-ablation and 6 monthly scans thereafter to evaluate treatment outcome. An FDG-PET scan was also requested at 6 months post-ablation.

Outcomes

Safety of the procedure was assessed by presence or absence of adverse events. Adverse events were recorded and classified in accordance with the Common Terminology Criteria for Adverse Events version 4.03[8].

Efficacy of the procedure was assessed by local tumour response to ablation and survival time. For MWA, the limited CT scan of the ablated site 24 h post-ablation served as the baseline scan that all subsequent follow-up scans were compared against; for RFA, the immediate post-ablation scan was used. Local progres-

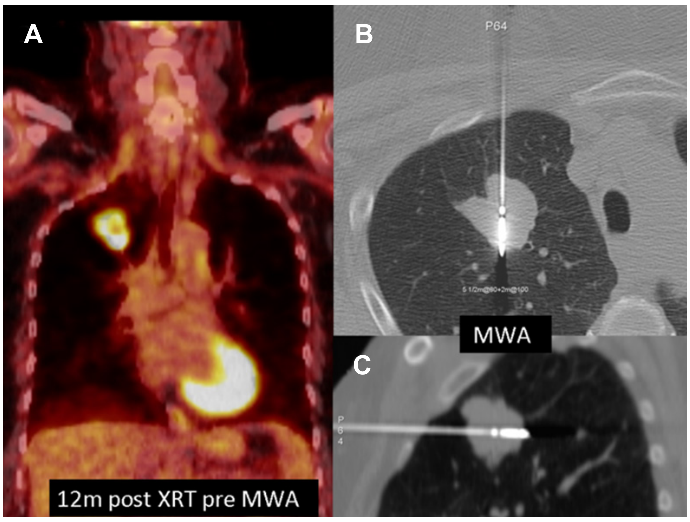

Figure 1. 57-year-old female with RUL SCC. A: Coronal FDG-PET scan 12 months post definitive radiotherapy (58 Gy) RUL T2N0 SCC; B, C: microwave antenna (Acculis standard pMTA) centrally within the tumour; a total of 7 min 30 s ablation time-5 min 30 s at 80 W followed by 2 min at 100 W. RUL: right upper lobe; SCC: squamous cell carcinoma

sion after initial ablation was defined as an increase in the size (maximum axial diameter) of the ablation zone on CT. Stability or decrease in size of the ablation zone on CT was considered complete ablation[9]. Patients were followed up until 30 Jun 2017. Patients were either alive, evidenced by a documented visit to an outpatient clinic, general practitioner or scan appointment after this date, or deceased, as recorded on the state health database. Follow-up periods were calculated from date of repeat ablation.

Statistical methods

The characteristics of patients and treatment outcomes were summarised using frequencies and percent for categorical variables and mean [standard deviation (SD)] or median [interquartile range (IQR) and range] for continuous variables. Kaplan-Meier survival estimates were produced for overall survival. STATA 15[10] was used for analyses.

RESULTS

Patient and tumour characteristics

From December 2009 to March 2017, 13 patients (6 male, 7 female) underwent repeat ablation of a lung tumour due to local progression after prior ablation(s) [Figures 1-5]. All prior ablations had been technically successful. Mean age at repeat ablation was 72 years (SD 11, range 53-88) [Table 1].

The ablated lung tumours consisted of: non-small cell lung carcinoma (NSCLC) (8 stage 1 NSCLCs, and 1 multifocal bronchioloalveolar carcinoma with bilateral lung involvement), metastatic colorectal adenocarcinoma (3) and metastatic pelvic sarcoma (1). Four of the NSCLC lesions had locally progressed post-radiotherapy and were subsequently referred for ablation.

Thermal ablation characteristics

Eleven of the 13 patients had repeat MWA; 7 patients after 1 prior MWA procedure, 2 patients after 2 prior MWA procedures, and 2 patients after 1 prior RFA treatment. The remaining 2 patients had repeat RFA after 1 prior RFA treatment. Nine of the 11 repeat MWAs were performed with the Acculis Microwave Tissue Ablation system (Angiodynamics, Latham, New York, USA), which operates at 2.45 GHz with a maximum power output of 140 watts; a standard antenna with a 16 mm active tip was used in these 9 cases. The remaining 2 repeat MWAs were performed with the HS Amica microwave system (HS Amica, HS Hospital

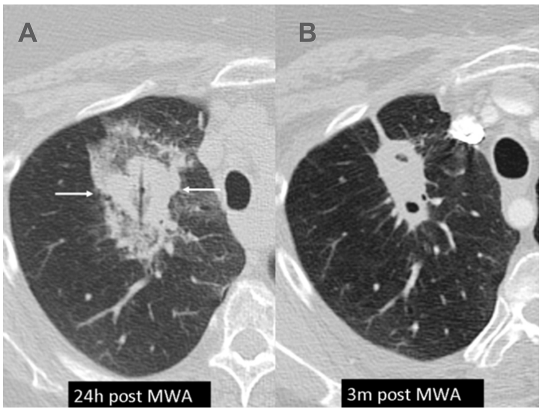

Figure 2. 57-year-old female with right upper lobe squamous cell carcinoma. Axial CT scan lung windows. A: 24 h post microwave ablation showing surrounding GGO, most narrow GGO zone medially and laterally (arrows); B: 3 months post microwave ablation showing satisfactory shrinking of ablation zone, small central cavities. GGO: ground-glass opacity

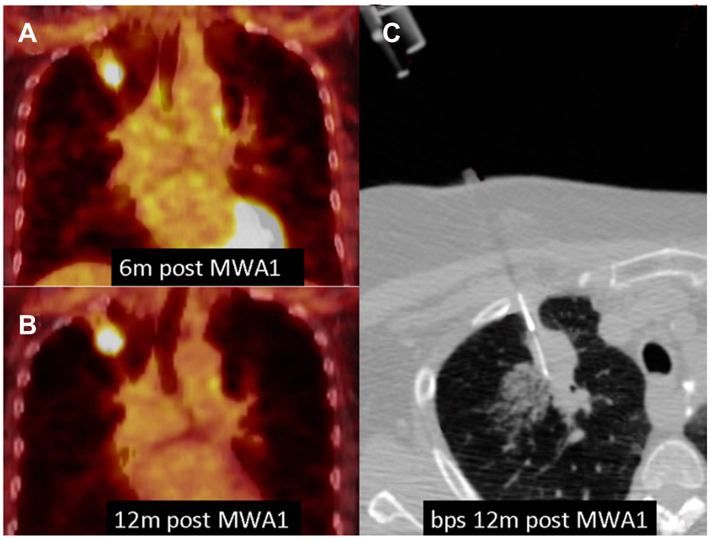

Figure 3. 57-year-old female with right upper lobe SCC. A, B: Coronal FDG-PET/CT scans 6 months and 12 months post microwave ablation showing residual FDG avidity increasing; C: CT guided core biopsy demonstrated local recurrence of SCC. CT guided core biopsy demonstrated local recurrence of SCC. SCC: squamous cell carcinoma

Service, Rome, Italy), which operates at 2.45 GHz with a maximum power output of 140 watts; a 16 gauge 15 cm probe was used in both cases. Of the 2 patients treated with repeat RFA, the Cool-tip internally cooled electrode system (Cool-tip, Valleylab, Boulder, Colorado, USA) with a 3 cm active tip was used for one patient, and the Rita Starbust XL Electrosurgical device (Rita Medical Systems, Mountain View, California, USA, now Angiodynamics) was used for the other patient.

Procedure tolerability and complications

Repeat ablation procedures were generally safe, without major adverse events [Table 2]. Median length of hospital stay was 2 days (IQR 1-2, range 1-7) [Table 2]. All but 1 (8%) of the repeat ablation procedures were technically successful. One procedure was complicated by intraprocedural pneumothorax, which enlarged during the procedure, prompting a request from the anaesthetic team to abort the procedure given the patient's comorbidities of chronic obstructive pulmonary disease on home oxygen, obstructive sleep apnoea and morbid obesity. The pneumothorax was aspirated twice during the procedure, and required chest tube

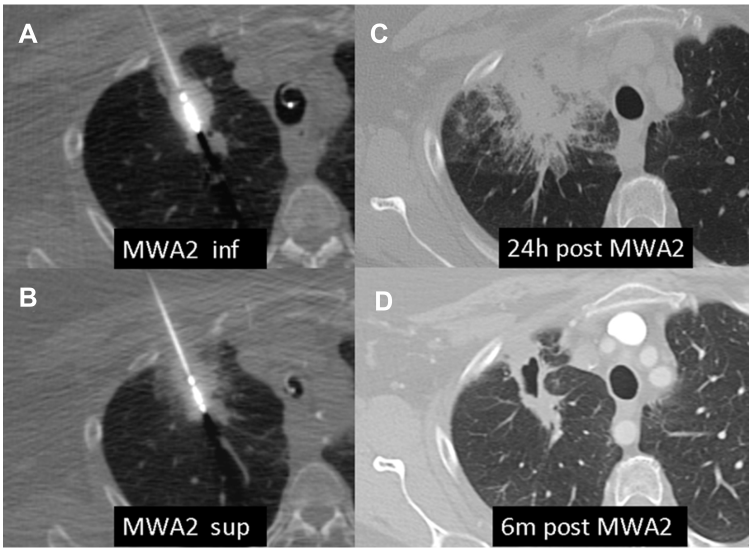

Figure 4. 57-year-old female with right upper lobe squamous cell carcinoma. A, B: Repeat microwave ablation, 2 overlapping ablation cycles; C: axial CT 24 h post re-ablation shows circumferential ground-glass opacity of at least 1 cm; D: axial CT 6 months post re-ablation shows significant shrinking of ablation site with central cavitation

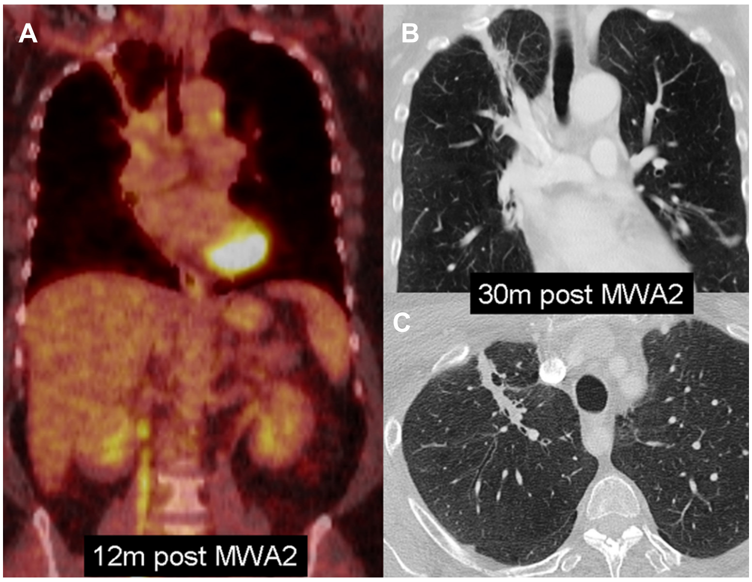

Figure 5. 57-year-old female with RUL squamous cell carcinoma. A: Coronal FDG-PET/CT shows no residual FDG uptake at the RUL ablation site 12 months post re-ablation; B, C: coronal and axial CT scan lung windows 30 months post re-ablation shows band-like scarring/atelectasis at site of previous tumour. RUL: right upper lobe

insertion after the procedure, which resolved the pneumothorax. The patient subsequently had an uneventful recovery.

There were no intraprocedural deaths. Five (38%) patients experienced pneumothorax from the procedure, 3 (23%) of whom required chest tube insertion [Table 2]. There was 1 (8%) death within 30 days of the procedure (repeat ablation of metastatic pelvic sarcoma), although the cause of death and relation to the procedure were unknown. The patient had been discharged the day after an uneventful ablation procedure and died at home two days after the procedure of a sudden death during the night[11]. The presumed cause

Table 1. Patient and lung tumour characteristics at repeat ablation

	Total (*n* = 13)
Age (years), Mean (SD)	72 (11.0)
Sex	
Female	7 (54)
Male	6 (46)
Tumour type	
Non-small cell lung carcinoma	9 (69)
Colorectal adenocarcinoma	3 (23)
Pelvic sarcoma	1 (8)
Type of prior ablation/s	
MWA	9 (69)
RFA	4 (31)
Number of prior ablation/s	
1	11 (85)
2	2 (15)
Radiotherapy prior to ablations	
No	9 (69)
Yes	4 (31)
Lobe	
LLL	2 (15)
LUL	8 (62)
RLL	1 (8)
RUL	2 (15)
Repeat ablation modality	
MWA	11 (85)
RFA	2 (15)
Diameter (mm)[†], median (IQR)	28.2 (22.0-40.0)
Number of ablation cycles	
1	1 (8)
2	8 (62)
3	4 (31)
Maximum power used (Watts) (MWA, *n* = 11)	
60-80	3 (27)
100-120	8 (73)
Total ablation duration (minutes) (MWA, *n* = 11), median (IQR)	4.5 (4.0-6.0)

[†]longest axial diameter in millimetres, immediately prior to repeat ablation. Data are presented as *n* (%) for categorical variables and as mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables. MWA: microwave ablation; RFA: radiofrequency ablation; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RLL: right lower lobe

of death was pulmonary embolism or myocardial infarction, however autopsy was declined and the cause of death was not definitively determined[11].

Response to treatment

Only 12 patients had follow-up imaging performed. The 1 patient without follow-up imaging had died 2 days after the procedure. Median length of CT follow-up was 26 months (range 3-62), and median length of FDG-PET follow-up was 6 months (range 0-26). Ten of twelve (83%) patients had complete ablation from their repeat ablation procedure. Two of twelve (17%) had local progression [Table 2], one of whom had the technically unsuccessful repeat ablation procedure. Time to first detection of local progression on imaging for the 2 patients with local progression were 8 and 27 months respectively.

Six of twelve (50%) patients had nodal or distant metastasis on follow-up imaging. Four of these patients had subsequent chemotherapy (the 2 patients in the local progression group, and 2 patients in the complete ablation group). Median time to first detection of metastasis on imaging was 20 months (range 11-36).

Survival

Of all 13 patients, 8 (62%) were alive [median follow-up 30 months (range 3-91)] and 5 (38%) had died (me-

Table 2. Repeat ablation treatment outcomes and complications

	Total (n = 13)
Technically successful	
No	1 (8)
Yes	12 (92)
Complications	
No	7 (54)
Yes	6 (46)
Pneumothorax (CTCAE grade 1)	1
Pneumothorax (CTCAE grade 1) and death within 30 days of procedure (CTCAE grade 5)	1
Pneumothorax (CTCAE grade 2)	2
Pneumothorax (CTCAE grade 2) and subcutaneous emphysema	1
Pleural effusion (CTCAE grade 1)	1
Length of hospital stay (days)	2 (1-2)
Post-ablation diameter (mm)[†]	54.0 (41.0-60.0)
Diameter on latest follow-up (mm) (n = 12)	38.5 (25.3-49.9)
Local tumour response to ablation (n = 12)	
Complete ablation	10 (83)
Local tumour progression	2 (17)
Nodal or distant metastasis on follow-up imaging (n = 12)	
No	6 (50)
Yes	6 (50)
Mortality	
Alive	8 (62)
Deceased	5 (38)

[†]For MWA, maximum axial diameter on 24 h post-ablation CT scan. For RFA, maximum axial diameter on immediate post-ablation CT scan. Data are presented as n (%) for categorical variables and as median [interquartile range (IQR)] for continuous variables. MWA: microwave ablation; RFA: radiofrequency ablation; CTCAE: Common Terminology Criteria for Adverse Events.

dian time to death 37 months (range 2 days-43 months). Median overall survival was 43 months (95% confidence interval 36-49).

In the 9 patients with NSCLC, 5 (56%) were alive [median follow-up 30 months (range 30-91)] and 4 (44%) had died [median time to death 38 months (range 27-43)]; all 4 had metastatic NSCLC at time of death. All were alive at 2 years.

All 3 patients with metastatic colorectal cancer were alive at the last date of follow-up [median follow-up 23 months (range 3-38)].

Local response to ablation and corresponding survival status at follow-up for all patients is summarised in Table 3.

DISCUSSION

We described the safety and efficacy of repeat ablation in a heterogeneous population of locally progressing lung tumours after prior ablation, including both primary and metastatic lesions. Repeat ablations were safe and well-tolerated, and often achieved local control despite local progression after prior technically successful ablation. Pneumothorax was the most common procedural complication, asymptomatic or manageable with chest tube insertion. Rate of pneumothorax requiring chest tube insertion (23% of procedures) was similar to that of other studies (11%-29%)[7,12-18]. Other reported complications of lung ablation include pain, post-ablation syndrome, pleural effusion, subcutaneous emphysema, pneumonia , bronchopleural fistula, pulmonary haemorrhage, haemoptysis, nerve injury and, rarely, death[7,11-18]. Our study had one 30-day post-procedural death, but the cause of death and relation to the procedure were unknown. Other studies have estimated the 30-day mortality rate after thermal ablation to be 0%-3%[12-15,19].

Table 3. Local tumour response to ablation and survival status at follow-up

Local response	Survival status		Total
	Alive	Dead	
Complete ablation	7	3	10
Local progression	1	1	2
No imaging follow-up	0	1	1
Total	8	5	13

While surgery is the treatment of choice in early stage NSCLC, many patients are not candidates for surgery due to comorbidities[1]. Percutaneous thermal ablation is a minimally invasive alternative treatment option with minimal impact on the uninvolved lung parenchyma and overall pulmonary function[20]. Our results demonstrate that even after failed initial attempt(s) at ablation, repeat ablation can achieve local control. Only 2 of our patients experienced local progression on follow-up imaging after repeat ablation. Two-year overall survival in our NSCLC patients after repeat ablation was 100%. Yang *et al*.[7] recently reported repeat MWA to be a safe and effective treatment for local progression of medically inoperable stage 1 NSCLC after initial MWA, with 21 of 24 (87.5%) patients achieving local control after repeat MWA, and with median overall survival 41.5 months after first MWA, similar to those treated with single MWA and with no local progression (median overall survival 48 months) at their institution. Our results support these findings that repeat thermal ablation is a safe and effective treatment for local progression of stage 1 NSCLC after initial ablation.

Thermal ablation may also be used for local control of secondary lung metastases. The goal in such patients is to improve patient quality of life and prolong survival. In a series of 566 patients with 1037 lung metastases of various primary origin, RFA treatment resulted in a median overall survival of 62 months, and a 4-year local control rate of 44.1%, with patients re-treated with RFA safely up to four times[9]. Our small sample of metastatic colorectal cancer patients re-treated with MWA all achieved local control and were alive after a median follow-up time of 23 months. The minimally invasive nature and repeatability of ablation are of utility in local control of lung metastases.

Six out of 12 patients had nodal or distant metastasis on follow-up imaging, with 2 of these patients demonstrating local progression at the ablation site, suggesting systemic disease progression despite local control in the other four patients. We believe offering repeat ablation for local control is still of value, as it is a minimally invasive technique which may improve patient quality of life and prolong survival, without significant increase in morbidity.

In this study, we defined local tumour response to ablation as based on increase, stability or decrease in size of ablation zone on CT[9]. FDG-PET scan findings are more difficult to interpret, as local uptake may be due to post-treatment inflammatory changes rather than local tumour progression, and this effect may last up to 12 months after ablation[21-23]. Additionally, false positive FDG-PET scans have been reported greater than 12 months after ablation[23]. The optimal timing of FDG-PET scan after ablation is controversial and not yet defined[24]. FDG-PET is likely a useful adjunct to CT in assessing local response to ablation, as well as for diagnosis of nodal or distant metastasis. However, further research is needed in imaging criteria to determine treatment response to ablation.

This study was limited by small sample size, heterogeneity of tumour size and histology, difference of ablation systems used and retrospective assessment. Additionally, as some patients had to travel long distances for their procedure and were not followed up by the respective teams they had been admitted under for their ablations, follow-up CT and FDG-PET scans were occasionally not performed at the requested time, although local tumour response to ablation was still able to be determined based on the most recent follow-up CT. Furthermore, some patients who had nodal or distant metastasis on follow-up imaging subsequently had chemotherapy, which may have influenced local response to ablation. In the future, larger studies should evaluate the effect of tumour type, and the use of other treatments such as chemotherapy, on response to repeat ablation.

In conclusion, despite these limitations, our study demonstrates that repeat MWA or RFA in locally progressing tumours after initial ablation attempt(s) may be generally safe, well tolerated, and often achieves local control. These findings should be validated in larger prospective studies.

DECLARATIONS

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Authors' contributions
Design, literature research, data acquisition, drafted manuscript: Zhao H, Steinke K
Data analysis: Zhao H, Okano S, Pelecanos A, Steinke K
Substantively revised manuscript: Zhao H, Okano S, Pelecanos A, Steinke K

Availability of data and materials
Patients were identified using the radiology thermal ablation database at the Royal Brisbane and Women's Hospital. Data were collected retrospectively through systematic review of patient charts and imaging. The de-identified data is available by contacting the corresponding author Associate Professor Karin Steinke.

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None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Ethics approval for this study was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/14/QRBW/553).

Consent for publication
All patients provided written, informed consent.

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Mini-invasive Surgery

Original Article

Open Access

Clinical feasibility of sphincter-preserving resection with transanal rectal dissection for low-lying rectal cancer in Japanese patients: a single-center cohort study

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Abstract

Aim: Recently, the transanal down-to-up rectal dissection, a new approach to improve the difficult total mesorectal excision (TME) for low-lying rectal cancer, has been popularized. This study assessed the long-term oncologic and functional outcomes after sphincter-preserving resection combined with transanal rectal dissection (TARD) under direct vision for both complete TME and preservation of the internal anal sphincter (IAS) as much as possible to clarify the clinical feasibility of this approach.

Methods: A prospective cohort study was conducted in 90 Japanese patients between April 2003 and March 2012.

Results: Abdominoperineal resection (APR) was needed in 17 patients (18.9%) including 14 salvage APRs. Local recurrences occurred in 5 sphincter-preserving resection patients (6.8%). No significant between-group differences were observed in overall survival or 5-year disease-free survival. A significant benefit of preserving the internal anal sphincter completely in sphincter-preserving resection was found on the Wexner incontinence score (P = 0.005), low anterior resection syndrome score (P = 0.002), and visual analogue scale (P = 0.047).

Conclusion: TARD, performed under direct vision for both complete TME and preservation of the IAS as much as possible in sphincter-preserving resections for low-lying rectal cancers in Japanese patients, does not negatively impact oncologic outcomes and could have the benefit of minimizing postoperative anorectal dysfunction by preserving the internal anal sphincter.

Keywords: Transanal rectal dissection, transanal total mesorectal excision, intersphincteric resection, sphincter-preserving resection, anorectal function outcomes, oncologic outcomes

INTRODUCTION

In surgery for rectal cancer, total mesorectal excision (TME)[1,2] and negative circumferential resection margins[3,4] are prerequisites for minimizing local tumor recurrence after surgery for rectal cancer. However, male sex, high body mass index, visceral obesity, a narrow pelvis, bulky tumor and an advanced T-stage pose technical challenges during surgery due to poor visualization of the mesorectal planes, especially with laparoscopic surgery[5,6]. Actually, the ALaCart[7] and ACOSOG Z6051[8] randomized controlled trials failed to show the noninferiority of laparoscopic surgery compared with open surgery for oncologic outcomes. Additionally, minimizing postoperative anorectal dysfunction has been a major matter in sphincter preservation for low-lying rectal cancer (LRC) near the anus. Intersphincteric resection (ISR) makes sphincter preservation possible for many patients with LRC[9]. Laparoscopic ISR has been shown to be more feasible and beneficial than open ISR[10]. Recently, a new approach, the transanal total mesorectal excision (TaTME), has attracted increasing attention as a promising technique for rectal cancer patients who may be poor candidates for total TME. A transanal approach has another benefit: the level of the distal resection margin is determined as the first step in the anal canal, taking care to preserve the internal anal sphincter (IAS) as much as possible for LRC near the anus.

More recently, TaTME has been shown to be feasible in a randomized trial in France[11], a case-matched study[12] and a meta-analysis[13]. However, its feasibility for those of Asian race, including Japanese patients, remains unclear. As the average body mass index in Japan increases each year[14,15], the transanal approach may represent a solution for obese Japanese patients with a narrow pelvis and a bulky mesorectum.

The aim of this study was to clarify the clinical feasibility of this new technique by analyzing the long-term oncologic and functional outcomes after sphincter-preserving resection (SPR) combined with transanal rectal dissection (TARD) under direct vision for both complete TME and preservation of the IAS as much as possible[16].

METHODS

Patients

The study was approved by the ethics committee of Toho University Omori Medical Center (No. 17-41). Informed consent was obtained from all patients in this study. All patients who underwent laparoscopic and open SPR combined with TARD for LRC from April 2003 to March 2012 were included in this prospective observational cohort study. We evaluated 90 patients undergoing laparoscopic and open SPR at our institution for the feasibility of TARD for LRC. The inclusion criterion was LRC located ≤ 5 cm from the anal verge. Patients of both sexes and various ages were included. The exclusion criteria for TARD included lesions classified as T4b or N2-3, lateral lymph-node involvement, and the presence of distant metastases. An immediate conversion to an abdominoperineal resection (APR) was performed if we observed any tumor invasion into the external anal sphincter or the levator ani muscle during the dissection of the internal anal sphincter and external anal sphincter muscles.

Surgical technique

The surgical technique for transanal retrograde dissection of the low rectum has been described previously[13] [Figure 1]. Briefly, the anal canal was exposed using a self-retaining retractor (Lone Star Retractor; Lone Star Medical Products Inc., Houston, TX). The distal aspect of the canal at the lower margin of the tumor was closed using purse-string sutures under direct visualization, and the anal canal was irrigated

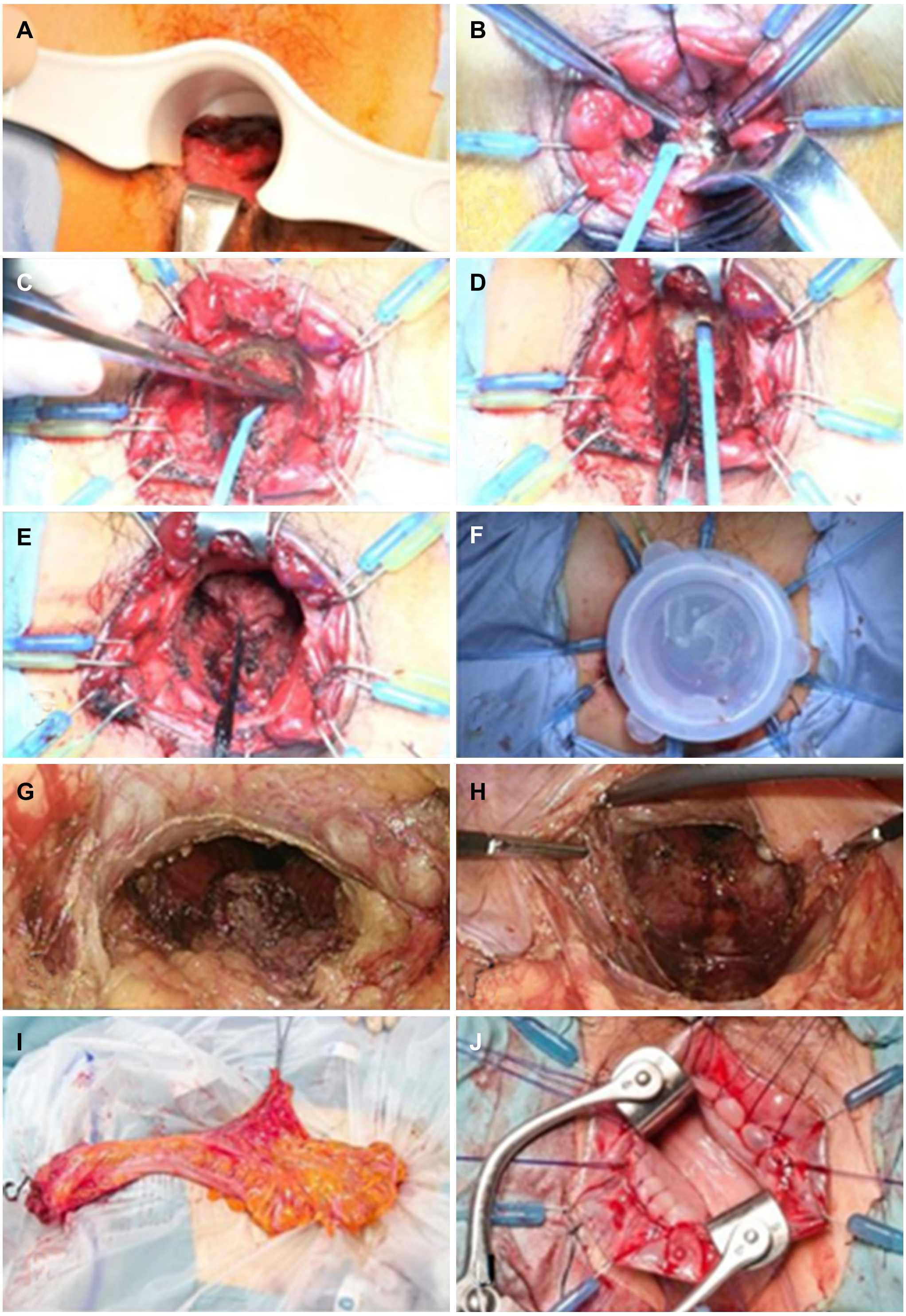

Figure 1. Photographs showing the procedure of an intersphincteric resection combined with transanal rectal dissection. A: Tumor was found at 4 cm from the anal verge, on the posterior side of the rectum; B-D: division of the rectum on the posterior side was performed, taking care to preserve the internal anal sphincter as much as possible. The rectum was circularly incised, closing the cut end with an interrupted suture, and the rectum (including the tumor) was mobilized proximally, exposing the levator ani muscle; E: the rectum, including the mesorectum, was divided and mobilized up to the peritoneal reflection on the anterior side and to the rectosacral ligament on the posterior side; F: a Lap Disc Mini (Hakko Co., Ltd, Chikuma-shi, Japan) was adapted to the anal canal to maintain pressure during laparoscopy; G-H: the rectum, including the entire mesorectum, was completely removed from the pelvic floor. To avoid nerve injury in this patient, Denonvilliers' fascia was not dissected; I: the colon and rectum were extruded through the umbilical wound and resected; J: a coloanal anastomosis was hand-sutured transanally

with 5% povidone-iodine solution. Division of the rectum on the posterior side was then performed, taking care to preserve the IAS as much as possible. The rectum was circularly incised, closing the cut end with an interrupted suture, and the rectum (including the tumor) was mobilized proximally, exposing the levator ani muscle. If the surgeon suspected tumor invasion into the dissected plane, the procedure was immediately converted to an APR. The rectum, including the mesorectum, was divided and mobilized up to the peritoneal reflection on the anterior side and to the rectosacral ligament on the posterior side. The 10 o'clock and 2 o'clock positions around the prostate were dissected on the abdominal part of the organ in order to avoid excessive dissection around these positions that could cause nerve injury and result in sexual dysfunction[17].

In the abdominal portion of a laparoscopic SPR, a Lap Disc Mini (Hakko Co., Ltd, Chikuma-shi, Japan) was adapted to the anal canal to maintain pressure during laparoscopy. A camera port was inserted into the umbilicus via a trocar; moreover, an operative port was inserted into the mid-lower abdominal region, and 2 additional operative ports were inserted into the left and right McBurney's points. During routine intra-abdominal exploration, gauze was placed on the dissected plane as a landmark that could be identified, through the peritoneum, from the anterior side of the rectum. The sigmoid and descending colon were completely mobilized from the subretroperitoneal fascia to ensure that the subsequent coloanal anastomosis was free of tension. The sigmoid colon and its mesentery were then removed, and the lymph nodes around the inferior mesenteric artery were dissected using a harmonic scalpel; additionally, the inferior mesenteric artery was ligated at a high level using an endoclip. Denonvillier's fascia was dissected, exposing, on the anterior side, the seminal vesicles and prostate gland in male patients and the posterior wall of the vagina in female patients. The lower rectum and mesorectum were mobilized from the sacrum, through the anus, on the divided plane between the visceral and parietal endopelvic fascia. The lateral ligaments of the rectum and the neurovascular bundle were gradually divided, using a harmonic scalpel, from the inner limit of the inferior hypogastric nerve fibers. The rectum, including the entire mesorectum, was completely removed from the pelvic floor. The colon and rectum were extruded through the umbilical wound and resected. A coloanal anastomosis was sutured transanally. Reconstruction was performed with a J-pouch or coloplasty, if possible. Finally, a diverting ileostomy was created; this was reversed 6 months after surgery. Although most parts of the procedure during the abdominal portion were performed by the surgical staff of the division of colorectal surgery, the anal portion of the surgery was performed only by the senior author (KF).

Definition of ISR

The ISR procedure partially or totally resects the IAS by dissecting the intersphincteric space. In this study, we defined partial ISR as a one-third resection of the upper part of the IAS between the dentate line and the intersphincteric groove, and we defined a massive ISR as a more than two-thirds resection between the dentate line and the intersphincteric groove. We take care to preserve the IAS as much as possible during division of the rectum. Rectal dissection beyond the dentate line with coloanal anastomosis was defined as a conventional coloanal anastomosis (conventional CAA).

Functional assessment

Anorectal function following ISR or conventional CAA was measured using structured questionnaires at regular intervals following closure of the diverting stoma. Patients answered questions on daily stool frequency and the presence of fecal urgency (incapacity to restrain defecation for more than 5 min). We also used the Wexner incontinence (WI) score[16], the low anterior resection syndrome (LARS) score[18], and a survey assessing the patients' satisfaction with their daily bowel-movement habits that employed a visual analogue scale (VAS). Complete incontinence was defined as a WI score of 20. In this study, the ISR patients were divided into 2 groups: partial ISR and massive ISR.

Postoperative follow-up

After surgery, patients were followed in the clinic every 3 months to be monitored for cancer recurrence and anorectal function. Blood tests at each visit included carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) levels. Patients were evaluated every 3 months using computed tomography or abdominal ultrasonography for the first 3 years and every 6 months thereafter. Local recurrence was defined as any recurrence that was diagnosed or suspected in the pelvis, either alone or with other metastases.

Function was assessed using a questionnaire that included questions on stool frequency and fecal urgency. We used the WI score and assessed patient satisfaction using the VAS score previously described. This questionnaire was administered by the medical staff to all patients who underwent SPR at all clinical follow-up appointments. We evaluated the effects of the degree of IAS resection on the patients' long-term anorectal function.

Statistical analysis

Data were analyzed using either the chi-squared test or Fisher's exact test. Continuous variables were compared using the Kruskal Wallis H-test. Survival rates were assessed using Kaplan-Meier curves and the log-rank test. A *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using Predictive Analytics SoftWare (PASW), version 18 (SPSS, Inc., Chicago, IL).

RESULTS

Patient characteristics

Ninety patients (63 male, 27 female) with a median age of 62 years (range 33-80 years) were enrolled. The median BMI was 22.5 kg/m^2 (range 16.7-32.9 kg/m^2). Fifteen patients (16.7%) had received preoperative chemoradiation therapy (pre-CRT). In this series, all tumors were designated as type II-III, according to Rullier's classification[19]. Seventeen patients (18.9%) required intraoperative conversion to APR: in 14 patients, this was because of the surgeon's suspicion for direct tumor invasion into the levator ani muscle, prostate, or vagina; in 2 patients, there was ischemia of the descending colon; and in 1 patient, anatomic disorientation occurred. In the 73 patients who underwent successful SPR, efforts were made to preserve the IAS as much as possible to avoid postoperative anorectal dysfunction. In 21 of these 73 patients (28.8%), the IAS was completely preserved, and the coloanal anastomosis was hand sewn; 33 patients underwent partial ISR, and 19 underwent massive ISR. According to Quirke's classification, the weighted mean of the quality of the mesorectum dissection was complete TME in 94.5% and nearly complete TME in 1.4%. Also, the rate of involvement of the circumferential resection margin was 2.7%.

The pathologic tumor-node-metastasis (pTNM) staging in the patients who underwent SPR was stage I in 27 patients (37.0%), stage II in 23 patients (31.5%), and stage III in 22 patients (30.1%). The pTNM staging of the patients who underwent APR was stage I in 3 patients (17.6%), stage II in 9 patients (52.9%), and stage III in 4 patients (23.5%). Because of a complete response to pre-CRT, pTNM staging could not be performed in 2 patients (1 in each group). Although in stage II and III advanced disease was observed more frequently in the patients who underwent APR, there was no statistically significant difference between the APR and SPR groups [Table 1].

Oncologic results

During a median follow-up period of 3958 days (range 2778-6583 days), recurrence developed in 13 of the SPR patients (17.8%) and in 5 of the APR patients (29.1%). Distant recurrence developed more frequently in the APR patients, while local recurrence occurred exclusively in those patients who underwent SPR [Table 2]. Local recurrences developed around the internal iliac artery in 4 patients and around the prostate in 1 patient. One patient with a local recurrence underwent pre-CRT because of locally advanced cancer (cT4N2M0), and the remaining 4 patients were diagnosed with clinical stage III disease [Table 3].

The 5-year overall survival rates were 88.1% and 87.5% in the SPR and APR groups, respectively. The 5-year disease-free survival rates were 85.0% and 80.8% in the SPR and APR groups, respectively. No significant

Table 1. Patient characteristics of the APR and SPR groups

	SPR (*n* = 73)	APR (*n* = 17)	*P* value
Gender (%)			0.256
Male	49 (67.1)	14 (82.4)	
Female	24 (32.9)	3 (17.6)	
Age, years (range)	61 (33-79)	69 (40-80)	0.013
BMI, kg/m^2 (range)	23.3 (16.7-32.9)	21.6 (17.5-32.8)	0.160
Pre-CRT (%)	14 (19.2)	1 (5.9)	0.286
Operation type			0.040
Open	33 (45.2)	13 (76.5)	
Laparoscopic	40 (54.8)	4 (23.5)	
Quality of TME (%)			1.000
Complete	69 (94.5)	17 (100)	
Near complete	1 (1.4)	0	
NE	3	0	
Circumferential resection margin (%)			1.000
Negative	68 (93.1)	17 (100)	
Positive	2 (2.7)	0	
NE	3	0	
Maximum tumor size in specimen, mm (range)	34.5 (8-109)		
Pathological TNM staging			0.243
I	27 (37.0)	3 (17.6)	
II	23 (31.5)	9 (52.9)	
III	22 (30.1)	4 (23.5)	
NE	1 (1.4)	1 (6.0)	

Data shown as median (range) or *n* (%). BMI: body mass index; Pre-CRT: preoperative chemoradiation therapy; TME: total mesorectal excision; TNM: tumor-node-metastasis; SPR: sphincter-preserving resection; APR: abdominoperineal resection; NE: not evaluated

Table 2. Recurrence after surgery

	SPR (*n* = 73)	APR (*n* = 17)	*P* value
Recurrence (%)	13 (17.8)	5 (29.1)	0.317
Local	5 (6.8)	0	0.248
Distant	8 (11.0)	5 (29.1)	
Liver	2	2	
Lung	5	1	
Other	1	2	
Median follow-up period, days (range)	3958 (2778-6583)		

Data shown as *n* (%).SPR: sphincter-preserving resection; APR: abdominoperineal resection

differences in either were observed between the 2 groups (P = 0.751 and P = 0.892, respectively). The 5-year overall survival rate in the patients who underwent SPR was 100% for those with stage I disease, 86.5% for stage II disease, and 72.1% for stage III disease [Figure 2].

Functional results

During a median follow-up period of 1450 days (range 475-2544 days), 11 patients did not respond to the questionnaire. Surveys were stopped in 4 patients because of cancer recurrence. Two patients did not consent to an ileostomal closure. One patient required a permanent colostomy because of a perineal hernia after a pelvic-bone fracture. Ultimately, anal function was assessed in 55 of the 73 SPR patients (75.3%): 18 conventional CAA patients, 22 partial ISR patients, and 15 massive ISR patients [Table 4]. The functional outcomes of the 3 groups are shown in Table 5.

A significant difference in the WI score (P = 0.005), LARS score (P = 0.002), and VAS score (P = 0.047) was observed between the 3 groups.

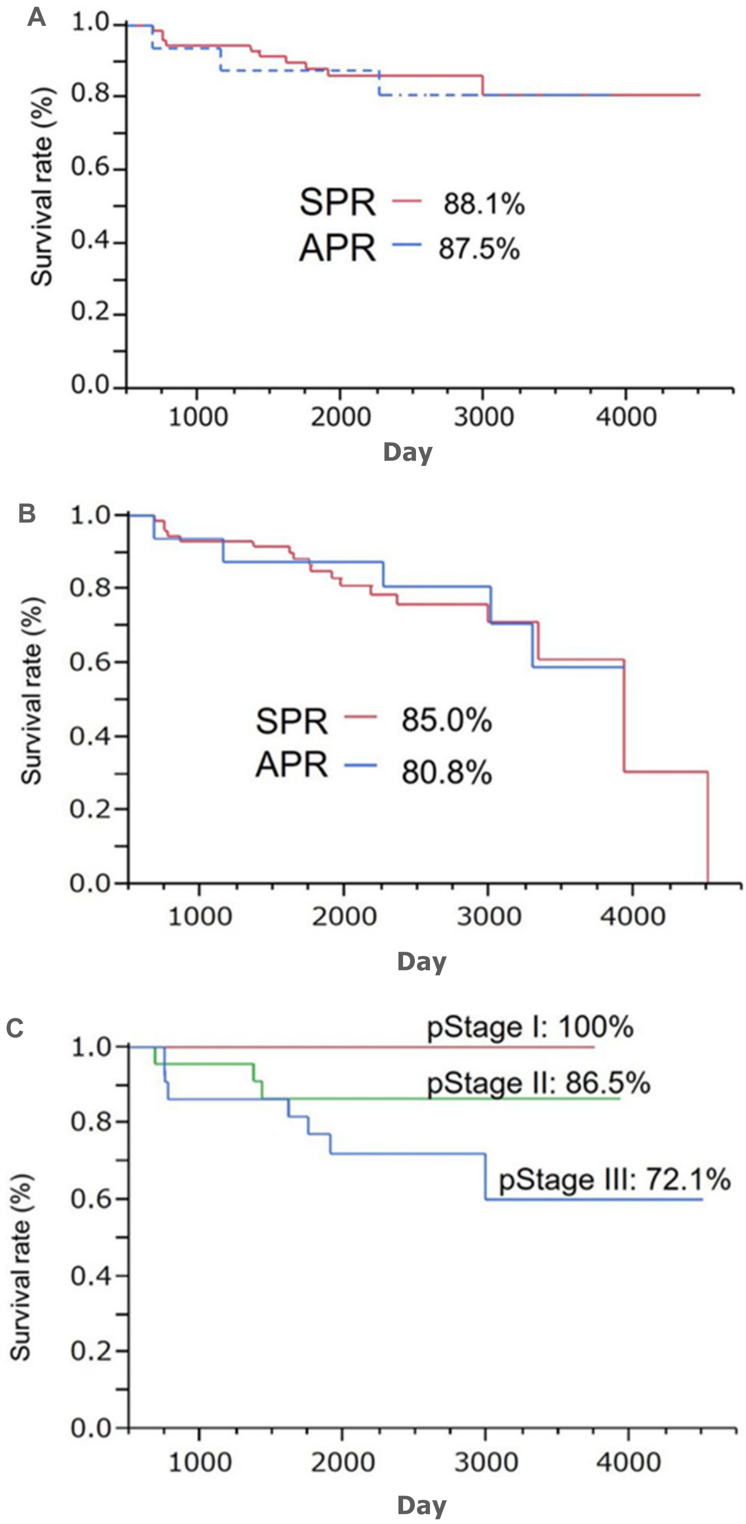

Figure 2. Kaplan-Meier survival rate in the sphincter-preserving resection and abdominoperineal resection groups. A: overall survival rate; B: disease-free survival rate; C: overall survival rate according to pathological stage in the sphincter-preserving resection group

DISCUSSION

Transanal approaches to pelvic dissection have attracted attention to improve oncologic and functional outcomes by providing better visualization and more accurate TME dissection. In 1984, Dr. Gerald Marks was the first surgeon to use a perineal approach to transanal dissection of the rectum for TME; his goal was to avoid leaving the patient with a permanent colostomy[20,21]. In April 2003, we implemented the TARD technique in laparoscopic SPR for LRC located ≤ 5 cm from the anal verge in order to achieve more accurate TME and to maintain the function of the IAS as much as possible after ISR[22]. A randomized trial showed that a transanal approach to TME was more effective than the conventional laparoscopic approach to TME in terms of negative circumferential resection margins and suggested that the perineal approach could be the new standard for laparoscopic SPR in Western patients with LRC[23]. However, in its long-term results, lower positivity of the circumferential resection margin did not translate into a decreased incidence of local recurrence[11]. Marks *et al.*[12] reported that the primary perineal approach reduces operative time and is associated with similar short- and long-term outcomes compared with the primary abdominal approach to laparoscopic ISR. On the other hand, two randomized controlled trials, the ALaCart[7] and ACOSOG Z6051[8] trials, failed to show the noninferiority of laparoscopic surgery compared with open surgery for oncologic outcomes. Two multi-center, randomized, controlled trials, COLORIII[24] and GRECCAR 11[25], will provide more definitive results.

The feasibility and benefit of this approach for Asian patients, including Japanese patients, should be evaluated. To our knowledge, although there are many reports of SPR including ISR in Japanese patients[26-35], ours is the first to describe the long-term oncologic and functional outcomes of SPR via the transanal approach in the Japanese population.

In the reports by Rouanet *et al.*[36], Denost *et al.*[23], Lacy *et al.*[37], Burke *et al.*[38], and Veltcamp Helbach *et al.*[39], CRM positivity was 2.5%, 4%, 6.4%, 4%, and 2.5%, respectively. In this series, 17 patients (18.9%) required conversion to APR. In 14 of these, salvage APR was performed because tumor invasion into the levator ani muscle, prostate, or vagina was suspected during rectal dissection. As final histopathology revealed a negative CRM for each of these patients, TARD could be a useful approach for clinical T4b tumors. A good CRM of 93.1% was shown in the SPR group as well. Patients who underwent SPR had an overall survival rate of 88.1% and a disease-free survival rate of 84.9% after 5 years. This was not significantly different from patients who underwent APR. These results show that TARD has a potential benefit of being able to allow immediate conversion to APR as a salvage procedure when tumor invasion to the rectal dissection plane is suspected during SPR for advanced disease categorized as type II-III according to Rullier's classification. Local recurrence occurred in 6.8% of the SPR patients during a median follow-up period of 3958 days (range 2778-6583 days); these findings are similar to those of Rullier *et al.*[19] who reported rates from 5% to 9% in 135 conventional CAA patients, 131 partial-ISR patients, and 55 total-ISR patients. For unclear reasons, local recurrence was only observed after ISR in this series. All patients with local recurrence were male with stage III disease, and 1 had received pre-CRT. Histologically, locally advanced disease was observed in most patients. No technical errors were reported in the operative records.

Postoperative anorectal function is a significant concern for patients undergoing SPR, including ISR. Although ISR has broadened the sphincter-preserving options for selected patients with LRC, impaired anorectal function after ISR remains a major problem. Many studies have found that patients undergoing SPR, including low anterior resection, conventional CAA, and ISR, are at risk for developing LARS (e.g., frequent bowel movements, urgency, and incontinence of flatus). A recent review found that, regardless of the use of preoperative irradiation, 0% to 5.9% of patients who undergo ISR require a colostomy for post-procedural anorectal dysfunction[40]. It is well known that the IAS plays an important role in fecal continence, and that extensive resection of the IAS during SPR is likely to impair anorectal function. Some risk factors associated with anorectal dysfunction after ISR include pre-CRT[41,42], total resection of the IAS[43-45], tumor level, height of the anastomosis[46], and patient age[30]. In this series, pre-CRT was administered to 14 patients with locally advanced disease. Pre-CRT has been shown to negatively affect postsurgical function[47,48].

Most researchers agree that anorectal dysfunction after ISR improves as time proceeds, but any remaining postoperative anorectal dysfunction after IAS resection is significant.

Table 3. Details of local recurrence after surgery

No.	Gender	Age (years)	cTNM	Pre-CRT	Surgical approach	Tumor size (mm)	pTNM	CRM	Lymphatic vessel invasion	Recurrence site	Treatment	Status
1	Male	46	T4N2M0	P (grade 2)	Open	70	T3N0M0	Complete	None	Lt-lateral lymph node	Chemo	Alive
2	Male	51	T3N1M0	N	Open	85	T4bN2bM0 (prostate)	Incomplete	Moderate	Lt-lateral lymph node	RT + Chemo	Dead
3	Male	63	T3N1M0	N	Open	60	T3N1bN0	Complete	Moderate	Rt-lateral lymph node	RT + Chemo	Dead
4	Male	63	T3N1M0	N	Open	75	T3N1bN0	Complete	Slight	Pelvis	Chemo	Dead
5	Male	59	T3N1M0	N	Laparoscopic	20	T3N2aM0	Complete	Slight	Prostate	RT + Chemo TPE	Alive

Pre-CRT: preoperative chemoradiation therapy; P: positive; N: negative; pTNM: pathologic tumor-node-metastasis; Chemo: chemotherapy; CRM: circumferential resection margins; RT: radiation therapy; TPE: total pelvic exenteration; Lt: left; Rt: right

Table 4. Characteristics of the CAA, partial ISR and massive ISR patients

	Conventional CAA (*n* =18)	Partial ISR (*n* = 22)	Massive ISR (*n* = 15)
Gender			
Male	13	17	7
Female	5	5	8
Age, years (range)	59 (46-79)	62 (34-77)	56 (33-70)
BMI, kg/m^2 (range)	22.1(16.5-32.9)	24.7 (16.9-31.2)	20.4 (18.3-26.5)
Pre-CRT (%)	3 (16.7)	5 (22.7)	1 (6.7)
Reconstruction			
Pouch	0	3	3
Straight	18	19	12
Complication related to anastomosis (%)	0	4 (18.2)	2 (13.3)
Prolapse	0	1	1
Anastomotic structure	0	3	1

Data shown as median (range) or *n* (%). BMI: body mass index; CAA: coloanal anastomosis; Pre-CRT: preoperative chemoradiation therapy; ISR: intersphincteric resection

Table 5. Long-term function after sphincter-preserving resection

	Conventional CAA (*n* = 18)	Partial ISR (*n* = 22)	Massive ISR (*n* = 15)	*P* value
Follow-up period, days (range)	1096 (475-2508)	1467 (748-2537)	1814 (728-2544)	-
Daily bowel movements	0.8	2.6	2.2	NS
Urgency (%)	1 (5.6)	6 (27.3)	4 (26.7)	NS
Fecal incontinence	0	2 (9.1)	1 (6.7)	NS
WI score	5 (0-14)	10 (0-20)	10 (5-20)	0.005
LARS score	28 ± 6	33 ± 9	36 ± 3	0.002
VAS score	7.8 ± 1.5	6.4 ± 2.9	6.6 ± 1.5	0.047
Complication related to coloanal anastomosis (%)	0	4 (18.2)	2 (13.3)	NS
Prolapse	0	1	1	
Anastomotic stricture	0	3	1	

Data shown as median (range) or *n* (%). CAA: coloanal anastomosis; ISR: intersphincteric resection; WI: Wexner incontinence; LARS: low anterior resection syndrome; VAS: visual analogue scale

In this series, we were able to preserve the IAS completely in 18 patients (28.8%) using the TARD technique; consequently, this might minimize postoperative anorectal dysfunction in these patients. These results show again the significance of preserving the IAS for anorectal function after surgery[49].

This study showed the clinical feasibility of TARD under direct vision in SPR for LRC. TARD could represent a step toward a minimally invasive, natural orifice, transluminal endoscopic surgery. However, this study is limited by its single-institution nature, its lack of a control group, and its small sample size. In addition, most TARD procedures were performed by a single surgeon (KF); therefore, the potential for selection bias is significant. Our data must be interpreted in the context of these potential biases. Recently, TaTME utilizing laparoscopic instruments has been developed as a novel alternative to intersphincteric resection that provides solutions to many of the limitations of TARD, as it is performed under direct visualization[50]. We recommend that further studies should be performed to confirm that transanal surgery is feasible and of benefit for Japanese and all Asian patients.

Using TARD under direct vision during laparoscopic and open SPR for LRC has no negative effects on oncologic outcomes. However, resection of the IAS should be avoided, where possible, to minimize anorectal dysfunction after ISR. This approach is feasible for Japanese patients with LRC. Further studies that compare TaTME utilizing laparoscopic instruments with conventional transabdominal TME are required to fully understand the risks and benefits of this approach for the Japanese and greater Asian populations.

DECLARATIONS

Authors' contributions

Conception and design of the study: Teramoto T
Collection and assembly of data: Shiokawa H, Ushigome M, Kaneko T, Kagami S, Koda T
Analysis and interpretation of data: Koike J

Availability of data and materials

The data is presented and kept by the author and is available for scrutiny.

Financial support and sponsorship

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

The Ethics Committee of Toho University Omori Medical Center (No. 17-41) approved the study, which was conducted in accordance with the Helsinki Declaration and the standards of the Ethics Committee. Written informed consent was obtained from all patients in this study.

Consent for publication

Not applicable.

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Mini-invasive Surgery

Original Article

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Effect of mental training on short-term psychomotor skill acquisition in laparoscopic surgery - a pilot study

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Abstract

Aim: The mental demands of laparoscopic surgery create a steep learning curve for surgical trainees. Experienced surgeons informally conduct mental training prior to starting a complex laparoscopic procedure. Reconstructing haptic feedback to mentally observe surgeon-instrument-tissue interaction is considered to be acquired only with experience. An experiment was devised to implement mental training for the haptic feedback reconstruction and its effect on laparoscopic task performance was observed.

Methods: Twenty laparoscopy novice medical students with normal/corrected visual acuity and normal hearing were randomised into two groups. Both groups were asked to apply a pre-established consistent force by means of retracting a laparoscopic grasper fixed to an electronic weight scale. Studied group underwent mental training while control group conducted a laparoscopic task as a distraction exercise. Accuracy of the task performance was measured as primary outcome. Performance between dominant and non-dominant hands was the secondary outcome.

Results: Baseline assessment of both dominant and non-dominant hands between groups were similar ($P > 0.05$). Mental training group improved their performance (0.66 ± 0.04) *vs*. (1.06 ± 0.14) with dominant hand ($P < 0.01$) and (0.73 ± 0.04) *vs*. (1.10 ± 0.20) with non-dominant hand ($P < 0.05$), when compared with control group.

Conclusion: In a laparoscopic task performance, skill transfer is significantly accurate if mental haptic feedback reconstruction is achieved through mental training.

Keywords: Mental training, target force, haptic feedback

INTRODUCTION

The physical and mental demands of laparoscopic surgery create a steep learning curve for surgical trainees. A two-dimensional image of the operative field produced by laparoscope increases mental workload of the surgeon as they estimate depth in real-time. A direct surgeon-tissue interaction is lost and replaced by a surgeon-instrument-tissue interaction, posing various disadvantages in terms of haptic stimulation; moreover, the nature of laparoscopic instruments diminishes the quality of tactile feedback sensed through surgeon's hands.

Haptic feedback is defined as a force perceived by the surgeon that acts in the direction opposite to which he or she applies traction. Tactile feedback is defined as a response which one experiences as touch and is a part of haptic feedback. The ability of the skilled surgeon to mentally reconstruct and experience tactile feedback provides a more accurate estimate of the amount of force required to apply onto human tissue during a surgical procedure. Simulating these modes of feedback during mental training is thought to reduce cerebral workload during a laparoscopic procedure, ultimately benefiting other aspects of the surgery by efficiently allocating mental capacity. This lead to the hypothesis that mental trainings could be implemented to improve mental reconstruction of haptic and tactile feedback in a surgical novice. This may aid in training and help reduce the learning curve for laparoscopic surgery.

While studying mental haptic feedback reconstruction, it was estimated that dominant hands and non-dominant hands play different roles and their influence on the task performance cannot be ignored. The dominant hand has better precision and fine motor movements. Therefore, in a laparoscopic surgery, it is traditionally used for manoeuvring instruments such as cutting hooks and needle holders. The non-dominant hand is largely involved in retraction of tissue, often to expose an area underneath. Most commonly, it is used to hold a tissue plane to assist in intracorporeal procedures such as laparoscopic suturing[1].

This pilot study aims to study the effects of mental training on a specific psychomotor skill acquired after a brief session of kinaesthetic learning.

METHODS

Mental training for skill acquisition was tested using a mixed-method design. Comparisons were made between subjects who underwent mental rehearsal and those who did not. The evidence of skill acquisition between the dominant and non-dominant hands was also studied.

Candidates

Twenty medical students with no prior laparoscopic experience were invited to participate in this study. Candidates were randomised into two groups; mental training and control. Both groups had equal proportions of left and right hand dominant, in addition to equal numbers of male and female participants. Each received the same introduction but candidates were not informed of their group allocation until they have done baseline assessment.

The studied group received a mental training for two minutes in the form of displayed instructions in specific order [Figure 1].

The control group underwent a simple laparoscopic distraction exercise [Figure 2]. The distraction exercise was designed to simulate realistic conditions in surgeons who do not conduct mental training. A laptop attached to an external webcam was held by the observer which displayed the working space for the

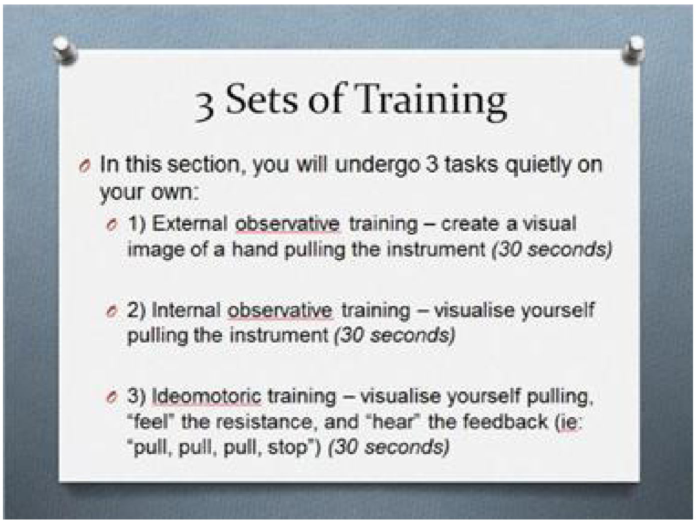

Figure 1. Mental training group instructions. (adapted from immenroth ,2007[4])

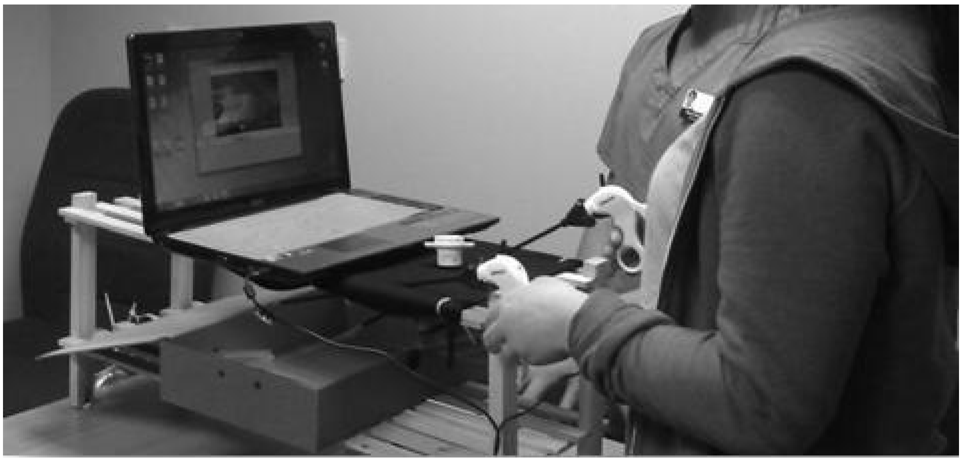

Figure 2. Laparoscopic distraction exercise setup

candidate. Two laparoscopic graspers are pushed through neoprene with a non-working laparoscopic port situated in between (to mark the area of pin swapping, when right hand instrument touches it). The task was to transfer three paper clips from one side of the working area to the opposite side, into a plastic container. Candidates were instructed to transfer these paper clips between their two laparoscopic graspers, i.e., from right to left. The camera was controlled by the observer.

Setup

A home-made laparoscopic setup was used for task performance [Figure 3]. This consisted of a two-tier shoe rack fitted with a large neoprene sheet overlying the top tier. A 5-mm trocar is pushed through the neoprene to accommodate the 5 mm laparoscopic grasper.

The ratchet grasper (Locking) is clamped to a piece of raw neoprene 5 mm × 1 mm × 60 mm. It was modified to allow attachment to the electronic weighing scale, without compromising its elastic behaviour when pulled upon [Figure 4]. A piece of neoprene was attached to weighing scale using cable tie. Neoprene has some degree of elasticity resembling human tissue, which was the reason for the selection of this material.

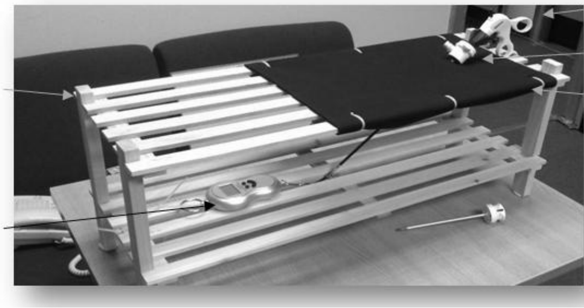

Figure 3. Home-made laparoscopic task setup

Figure 4. Mouth of grasper was locked to hold the piece of neoprene

Task

Each candidate was required to conduct a pulling action, applying a predetermined target force. The target force remained consistent in both groups and its numerical value was not disclosed to candidates. They were allowed to position themselves in their own comfortable standing. They were not in sight of the electronic weighing scale.

Target force

The electronic weighing scale in this study used measurements up to 40 kg, and poorly detected those under 0.5 kg. For the purposes of this study, the target force applied was measured in kilograms. Different human organs have different connective tissue strengths resulting in multiple target forces required to cause a tear. Although, it was beyond the scope and limitations of this study to check target forces on human tissue; nevertheless, to have a general idea about the laparoscopic pulling target force, a small-scale experiment was conducted on a pig's gall bladder with the same electronic scale. Twenty fresh gall bladders of adult pigs were acquired to check their wall strength. It was concluded that an average maximum pulling force beyond a mass of 1.1 kg was the tearing point of the pig's gall bladder tissue. Hence, the target force was set at 1kg for all participants, with an upper limit of 1.1 kg and a lower limit of 0.5 kg.

Kinaesthetic training

Each subject went through 5 attempts of kinaesthetic training, with both hands each. It started with the dominant hand, consisted of conducting five pulling motions with verbal feedback from the observer to notify when the target force has been reached. It was decided that under-traction of tissue was more acceptable than over-traction; therefore, if target value was exceeded, participants were notified to immediately restart the pulling motion.

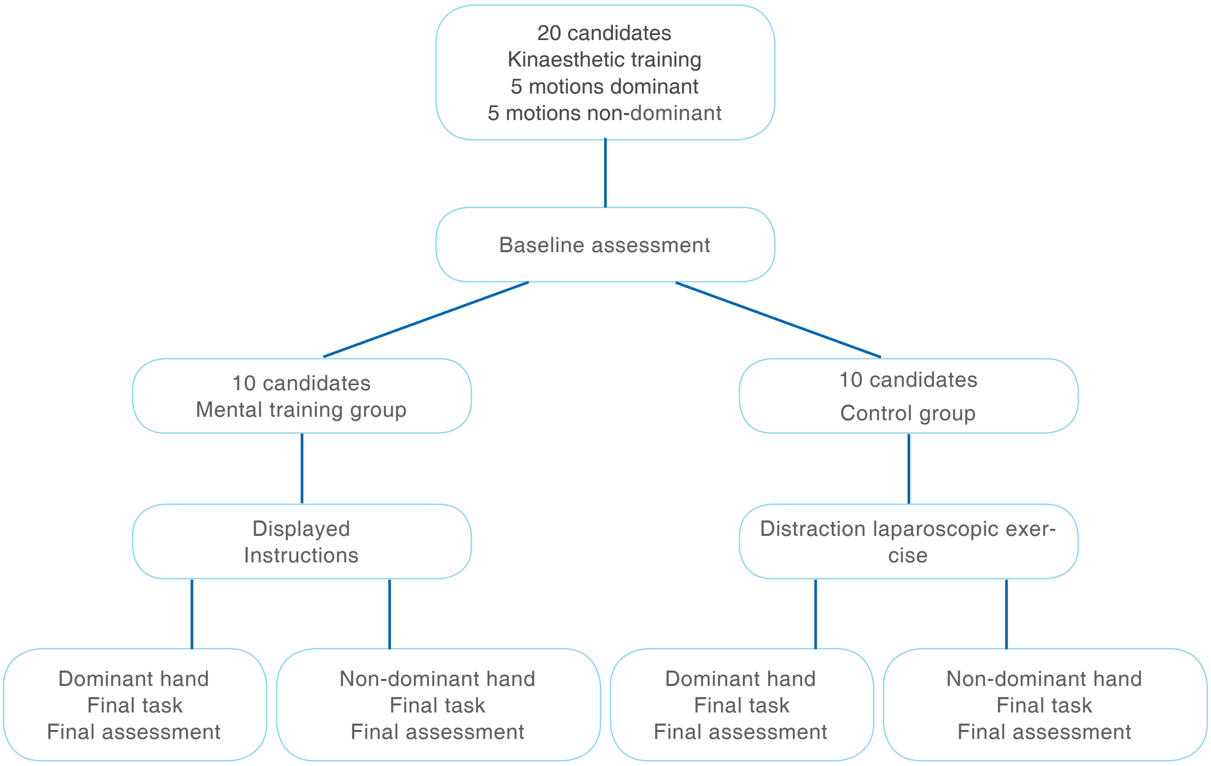

Figure 5. Trial profile

Baseline assessment

For baseline assessment, subjects were advised to pull the laparoscopic grasper in order to generate the target force of 1 kg. The outcome was recorded by an observer. Following the baseline assessment, the participants were informed of their allocated group.

Final assessment

An assessment similar to the baseline was conducted following the mental training or distraction exercise in both groups. The final assessment was conducted once. Candidates then repeated the final assessment with their non-dominant hands [Figure 5].

Statistical analysis

The statistical package for the Social Sciences Software (version 17.0.0, SPSS Chicago, IL, USA) and Excel (Microsoft Excel®, Microsoft Corporation, Redmond, Washington, USA) was used for data collection and interpretation. Based on previous similar studies[2,3] and literature review, power calculation suggested that 20 candidates should enable the detection of 20% difference between the two groups with 80% power at $P < 0.05$. Data for baseline and final assessment showed parametric distribution. Student t-test determined mean ± standard error of mean (s.e.m) with 95% confidence interval to highlight statistical difference between groups.

RESULTS

Results were analysed after plotting baseline and final assessment scores, resulting from target force applied [Table 1]. Improvement in precision was measured by the values of standard error of mean. The lower the standard error of mean, the higher the precision of the group.

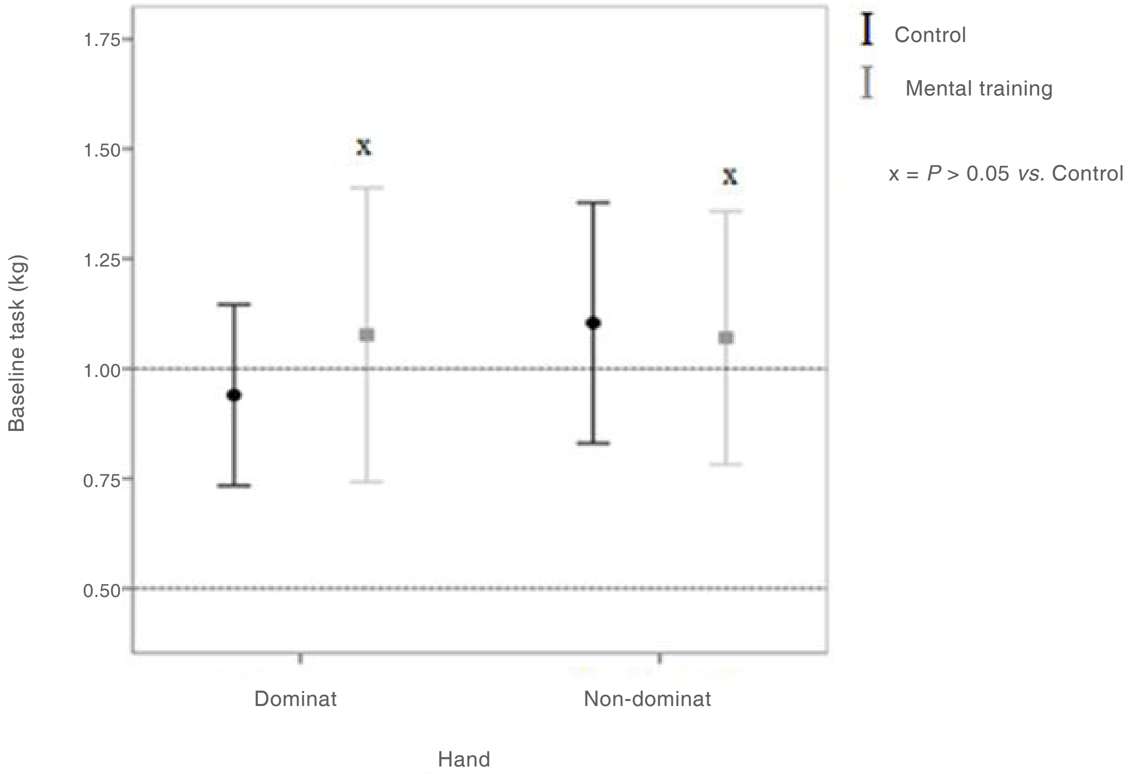

Figure 6. Mean ± sem baseline task (kg), control *vs*. mental training, 95% CI

DISCUSSION

Mental training has been shown to affect the way the brain distributes its workload. It increases performance in athletes and is an effective adjunct to training programmes for fighter pilots. Anecdotal evidence suggests that more experienced surgeons conduct informal mental training prior to starting a laparoscopic procedure[2]. Rehearsal in the mind involves recreating the environment of the surgical field. This includes reconstructing visual, auditory, and tactile feedback as expected throughout the procedure[3] Mental reconstruction of procedural conditions allows recollection of past experiences, which alert them to challenging areas of the operation. This instils an anticipatory attitude prior to starting the procedure[4]. Studies have noted that visual instrument-tissue interaction was easier to mentally reconstruct than tactile or haptic interactions felt when applying traction to tissue[5].

Results from this study revealed that the baseline scores for mental training group were similar to control group [Figure 6]. Candidates who conducted mental training had better precision than those who did not (0.66 ± 0.04 *vs*. 1.06 ± 0.14, $P = 0.01$ for dominant hand and 0.73 ± 0.04 *vs*. 1.10 ± 0.20, $P = 0.04$ for non-dominant hand), when compared with control group [Table 1]. Lower standard error of mean implied that the study group was more consistent in determining the target force than the control. This may be the result of a combination of conducting the mental training in addition to remembering the instructions given at the beginning of the session which encourages the participant to treat the equipment as in a real patient.

Dissimilar to control group where participants had a brief shift of focus, the mental training group heightened their vigilance against applying excessive traction. This advocated that mental training allowed candidates to evaluate their actions prior to applying the force. It also suggested that their self-evaluations

Table 1. Dominant vs. non-dominant hand, baseline and final results in both groups

Task: performing hand	Assessment stage	Groups	Mean ± 2 sem	*t*-test
Dominant hand	Baseline	Control	0.94 ± 0.09	*P* = 0.4
		Mental Training	1.07 ± 0.14	
	Final	Control	1.06 ± 0.14	*P* = 0.01
		Mental Training	0.66 ± 0.04	
Non-dominant hand	Baseline	Control	1.10 ± 0.12	*P* = 0.8
		Mental Training	1.04 ± 0.12	
	Final	Control	1.10 ± 0.20	*P* = 0.04
		Mental Training	0.73 ± 0.04	

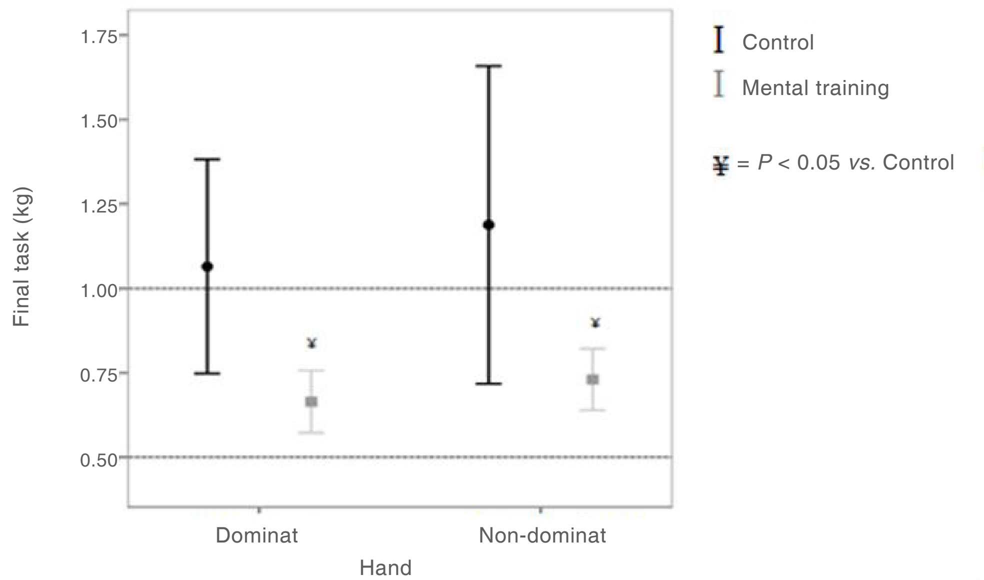

Figure 7. Mean ± sem Final task (kg), control *vs*. mental training, 95% CI

were consistent, indicating that under-traction will be more likely to happen than over-traction. Inferring from the data, iatrogenic tearing of tissue is less likely to occur in the mental training group. Accuracy remained an issue in control group in the form of over traction for both dominant and non dominant hands [Figure 7].

The method used to conduct this pilot study was based on simple principles of learning, training and observing the effects. Baseline and final assessments allowed an objective measure of each candidate's performance on a general scale. The simplistic nature of the study meant that the number of variables which could affect the results and create bias were limited. Aside from the technical challenges, the main improvement to this experiment would be to utilise a blindfold to allow complete exclusion of the visual senses during training. This study also highlighted the need for future research studies to understand required pulling target force for each part of human tissue. This knowledge could potentially be translated in developing new haptic communication in laparoscopic instruments.

DECLARATIONS

Author's contributions

Concept: Shariffudin AM, Alijani A, Riaz MK
Data collection, compilation: Shariffuddin AM, Riaz MK, Tang B
Manuscript writing: Riaz MK, Shariffuddin AM

Manuscript editing: Riaz MK, Shariffuddin AM, Tang B, Alijani A

Availability of data and materials
Data source is available with dr-riaz@doctors.org.uk in excel sheet form.

Financial support and sponsorship
This research work was supported by facilities and laparoscopic equipment from Cuschieri skills centre, university of Dundee.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical approval and consent to participate
As per university of Dundee research guidelines, ethical approval was not required for this study.

Consent for publication
Not applicable.

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Mini-invasive Surgery

Review

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Open or laparoscopic resection: does approach matter?

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Abstract

In colon cancer surgery, laparoscopic resection is a safer and more feasible method than open resection; however, despite its increasing popularity in recent years, laparoscopic approaches for the treatment of rectal cancer have not become a standard therapy option, due to the technical difficulties in gaining access to the deep and narrow pelvis and the steep learning curve. Multiple randomized trials found that short-term oncological outcomes and perioperative mortality and morbidity were comparable between laparoscopic and open rectal surgery, whereas comparative data between the two approaches. Comparative data between the two approaches on long-term oncological outcomes remain limited. In this review, we summarize the current status of laparoscopic surgery in rectal cancer in the light of recent studies.

Keywords: Laparoscopy, rectal cancer, oncological outcome, physiological outcome

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers worldwide and is responsible for approximately 750,000 cancer-related deaths annually[1]. Approximately 30% of colorectal adenocarcinomas originate from the rectum. In a multidisciplinary approach that combines chemotherapy with radiotherapy for the treatment of colorectal cancer, surgery remains the primary treatment option. The most significant improvement in rectal surgery was the widespread implementation of the total mesorectal excision (TME) technique, first described by Heald *et al.*[2] in 1982, which led to a reduction in locoregional recurrence rates from 25% in the 1980s to under 4% today[1].

The first successful use of laparoscopy in colorectal surgery was by Jacobs *et al*.[3], published in 1991. Laparoscopic surgery has numerous benefits, such as shorter length of hospitalization, reduced postoperative pain, and improved recovery[4-6]. Although many studies showed that the outcomes of laparoscopic and open colon surgery were similar[6,7-10], similar comparative outcomes have not been clearly demonstrated in laparoscopic rectal surgery. Concerns regarding laparoscopic rectal surgery are port-site and abdominal wall metastases and local oncological clearance[11-15]. In addition, laparoscopic rectal surgery has a challenging learning curve because of the deep and narrow pelvis and its assist-dependent procedure[16].

Current data comparing long-term oncological outcomes between open and laparoscopic rectal surgery are insufficient; therefore, laparoscopy is not accepted as a gold standard in rectal surgery. This review aims to summarize the oncological and physiological outcomes with laparoscopic and open rectal surgery based on the results of recent studies.

Importance of TME

Significant improvements were observed in oncological outcomes with TME since its introduction by Heald *et al*.[2] in 1982 and subsequent standardization in rectal cancer surgery. With the TME technique, the locoregional recurrence rate of 25% in the 1980s has been successfully reduced to 4% currently. Nagtegaal and van Krieken[17] reported that the local recurrence rate of 36% with incomplete mesorectal excision was decreased to 20% with complete TME. Kapiteijn *et al*.[18] compared the outcomes of conventional rectal surgery and TME and found that both local control and survival were improved in the TME group.

TME should be routinely performed to improve oncological results in both laparoscopic and open rectal surgery. Laparoscopic TME is a difficult technique to implement in the deep and narrow pelvis and has a steep learning curve. Several studies reported that at least 50 laparoscopic TME should be performed to achieve proficiency and consistent results[19-21], and the conversion rate decreases between 151 and 200 cases. Male sex and T staging of cancer are major risk factors affecting the learning curve[14]. The most important concerns regarding laparoscopic TME are postoperative morbidity and oncological outcomes. One of the most important steps for the correct implementation of TME is dissection of the mesorectum from the parietal and visceral fascia. Laparoscopy provides visualization of this plan and neurovascular structures through a magnified and clean vision.

Short-term oncological outcomes

The use of TME for rectal cancer has led to many favorable results. Blunt dissection commonly performed in the pelvis before the TME era often resulted in inadequate resection of the mesorectum. Quirke *et al.*[22] reported lateral surgical margin positivity in 14 of the 52 patients who achieved surgical cure and a local recurrence of 85% in those with positive margins. In contrast, in 1998, Heald *et al.*[23] reported 5- and 10-year local recurrence rates of only 3% and 4%, respectively, among 405 patients who underwent curative resection with TME; the 5- and 10-year disease-free survival rates were 80% and 78%, respectively, in this cohort. In a recent study by Maurer *et al.*[24], where the patients were followed for a minimum of 7 years, TME reduced rectal cancer recurrence from 20.8% to 5.9%.

Local recurrence is closely associated with several objectively measurable oncological parameters such as completeness of TME, involvement of the circumferential surgical margin (CRM), and number of harvested lymph nodes (HLNs). Prospective randomized trials included Colorectal Cancer Laparoscopic or Open Resection (COLOR) II trial, Conventional versus Laparoscopic-assisted Surgery in Patients with Colorectal Cancer (MRC CLASICC) trial, Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN) trial, ACOSOG Z6051 trial, Australian Laparoscopic Cancer of the Rectum (ALaCaRT) trial; retrospective studies, and meta-analyses evaluated the oncological outcomes of open and laparoscopic rectal surgery. In retrospective studies, laparoscopic rectal surgery was reported to be a generally safe and feasible procedure[25,26].

In the randomized COLOR II trial including 1103 patients with rectal cancer, although the duration of laparoscopic surgery was longer than that of open surgery (240 min *vs.* 188 min), blood loss was significantly less (200 mL *vs.* 400 mL), and the length of hospital stay was shorter (8 days *vs.* 9 days)[27]. There were no significant differences in the rate of CRM positivity, number of HLNs, or distal surgical margins between the two groups.

In the CLASSIC trial that included 27 UK centers and 381 patients with rectal cancer were randomized to open (n = 128) and laparoscopic (n = 253) surgery groups[6]. The rate of conversion to open surgery was 34%, whereas perioperative morbidity did not differ between the two groups. There was a nonsignificant increase in CRM positivity in the laparoscopic anterior resection group compared with the open surgery group (12% *vs.* 6%), suggesting a slight increase in the risk of recurrence. The 3- and 5-year follow-up studies of all rectal cancer patients revealed that there were no differences in local or distant recurrence rates between the laparoscopic and open surgical groups[28,29].

In the COREAN trial including 340 patients with locally advanced rectal cancer (T3N0-2) from three centers were randomized to open (n = 170) and laparoscopic surgery (n = 170) groups, and all patients received neoadjuvant chemoradiotherapy[30]. The rate of conversion to open surgery was 1.2%, and no differences between the two groups were observed in terms of postoperative morbidity, mortality, CRM positivity, or TME quality.

The ACOSOG Z6051 trial recruited stage IIA or III rectal cancer patients with a tumor ≤ 12 cm from the anal verge after neoadjuvant therapy. The trial was powered to detect the noninferiority of laparoscopic surgery[31]. Conversion to open surgery occurred in 11.3% of the patients. The authors demonstrated that there were no differences in radial or distal margin positivity or complete or near-total TME between the laparoscopy and open surgery groups.

The design of ALaCaRT trial was similar to that of ACOSOG Z6051, recruiting T1-3 and N0-2 rectal cancer patients with a tumor ≤ 15 cm from the anal verge to assess the noninferiority of laparoscopic surgery[10]. Although the length of laparoscopic surgery was longer, the blood loss was less in this group. There is no difference in the completeness of TME between the laparoscopic and open surgery groups (82% *vs.* 89%), CRM positivity was observed in 7% and 3% of the laparoscopy and open surgery group patients, respectively (P = 0.06), and the rate of conversion to open surgery was 9%. In this study, the laparoscopy group, especially those with large T3 tumors, failed to meet the noninferiority criteria. The controversy of this study with COREAN and COLOR II trials raised the question of whether there were any indications for laparoscopy in lower rectal cancers and locally advanced disease.

A prospective nonrandomized study by Lujan *et al.*[32] including 4405 patients from 72 centers who were divided into the laparoscopic (n = 1387) and open surgery (n = 3018) groups showed that the laparoscopy group had less hospitalization time, blood loss, and postoperative morbidity compared with the open surgery group. There was no significant difference in the number of HLNs between the two groups (laparoscopy *vs.* open, 14.5 *vs.* 14.7). The CRM and the distal margin involvement were significantly better in the laparoscopic group (P < 0.05), but the completeness of TME was significantly better in the open surgery group (P < 0.05).

In a two-center prospective study by Ströhlein *et al.*[33] laparoscopic surgery was associated with faster recovery and shorter hospital stays than open surgery. There is a significant difference in the number of HLNs between the laparoscopic and the open surgical groups (13.5 *vs.* 16.9; P = 0.001); however, no differences local recurrence or metachronous metastasis were observed between the two groups.

In summary, these trials demonstrated that there were no differences in local tumor clearance, number of HLNs, or tumor recurrence rates between the two surgical approaches in patients with rectal cancer.

Table 1. Randomized trials comparing oncological outcomes with laparoscopic and open surgery

Study	No. of patients (L/O)	Follow-up (months)	Local recurrence (months) (L/O) (%)	Overall survival (months) (L/O) (%)	Port site recurrence (%)
Braga *et al*.[35]	83/85	54	4/5.2	No difference	NA
Jayne *et al*.[28]	253/128	56	9.4/7.6	60/53 (5 years)	2.4
Green *et al*.[36]	253/128	63	No difference	83/66 months (median overall survival)	NA
Ng *et al*.[34]	40/40	76	2.8/8.9	86/91 (5 years)	0
Ng *et al*.[37]	51/48	90	5/11	75/77 (5 years)	0

L: laparoscopy group; O: open surgery group; NA: not available

Laparoscopic TME for cancer is technically feasible, with acceptable complication rates and short-term oncological outcomes that are comparable with those of open surgery.

Long-term oncological outcomes

The few randomized trials comparing long-term outcomes after laparoscopic and open TME consistently reported that laparoscopic and open TME were associated with similar oncological outcomes[28,34-37]. A summary comparison of oncological outcomes between laparoscopic and open TME in randomized comparative trials are presented in Table 1[38].

Ng *et al*.[37] investigated patients with rectal cancer who underwent laparoscopic (n = 51) or open abdominoperineal (n = 48) resection in a single-center prospective randomized trial. In this trial with a median follow-up duration of 90 months, the 5-year survival rates were 75.2% and 76.5% in the laparoscopic surgery and the open surgery groups, respectively. Another randomized trial in 2014, again by Ng *et al*.[34], found that the 5-year survival rates were 86% in the laparoscopic surgery group and 91% in the open surgery group during a median follow-up of 76 months. However, the number of patients receiving neoadjuvant treatment was not stated in neither of the studies; both of which included a relatively small number of patients. However, the results of both studies supported that the oncological outcomes of laparoscopic and open TME were comparable.

Bonjer *et al*.[9] published the long-term results of the COLOR II trial in 2015. At the end of the 3-year follow-up, the disease-free survival rates of the laparoscopic and open surgery groups were 74.8% and 70.8%, respectively, and there was no significant difference in overall survival between the laparoscopic and the open surgery groups (86.7% and 83.6%, respectively). These results indicated that laparoscopic surgery was a suitable and valid method in rectal cancer that did not invade the surrounding tissues.

In the CLASSIC trial cohort, the 3-year overall survival rate of the laparoscopic surgery group was not worse than that of the open surgery group (68.4% and 66.7%, respectively, P = 0.55)[6]. There was also no statistically significant difference in disease-free survival between the two groups (67.7% and 66.3% in open and laparoscopic surgery, respectively). The long-term results reported by Green *et al*.[36] revealed that the median overall survival of patients who underwent surgery for rectal carcinoma was 73.6 months and that there were no significant differences in the median overall survival (82.7 and 65.8 months) or the disease-free survival (67.1 and 70.6 months, P = 0.925) between the open and laparoscopic surgery groups, respectively. Furthermore, there were no differences in local, wound, or port recurrent rates between the two groups. The authors concluded that laparoscopic surgery should be preferred for early functional recovery without adversely affecting long-term survival outcomes.

Evaluation of the 3-year disease-free survival rates of the COREAN trial found no difference between the open and laparoscopic surgery groups (72.5% *vs*. 79.2%), and neither the 3-year overall survival nor the local recurrence parameters exceeded the 15% noninferiority limit[39].

A prospective study by Ströhlein *et al.*[33] reported 5-year local recurrence rates of 6.9% and 9.5% with laparoscopic and open surgery, respectively. Additionally, there were no significant differences in 5-year survival rates based on the disease between the two groups (open *vs.* laparoscopic; stage I, 75.2% *vs.* 85.4%; stage II, 73.4% *vs.* 66.7%; stage III, 51.3% *vs.* 60.1%). Similarly, Laurent *et al.*[40] found no significant differences in 5-year local recurrence, disease-free survival, or overall survival rates between the laparoscopy and open surgery groups.

In summary, further randomized clinical trials are necessary for complete elucidation of the feasibility of laparoscopic surgery in rectal cancer. Additionally, the anticipated publication of the long-term results of the ACOSOG Z6051 and ALaCaRT trials should provide further insight regarding the implementation of laparoscopic surgery for rectal cancer.

Sexual and urinary dysfunction associated with laparoscopic surgery

Normal bladder and sexual function is controlled by sympathetic input from the superior hypogastric plexus and parasympathetic input from the pelvic splanchnic nerves, which are susceptible to injury during mesorectal resection. Injury to the sympathetic supply results in bladder instability and ejaculatory difficulties, whereas injury to the parasympathetic supply results in poor detrusor contraction and erectile dysfunction[41,42].

The incidence of urinary and sexual dysfunction after open TME is significantly high[43-46]. In laparoscopic TME, preservation of the nerves can be achieved by magnifying the images. In a series of 274 patients reported by Runkel and Reiser[47], only 1.8% of the patients required prolonged urinary catheterization postoperatively. In other studies, the rate of urinary dysfunction after laparoscopic TME ranged from 6% to 15%[48-52], and the incidence of dysfunction ranged between 5% and 28% in males who were sexually active before laparoscopic TME[34,47,51,52].

Asoglu *et al.*[52] reported that the rate of reduction in sexual function among female patients was 7%. In that comparative study, laparoscopic TME was associated with significantly less sexual dysfunction in both male and female patients, and the rate of urinary dysfunction was similar between the laparoscopic and open TME groups.

In a study on data from 247 patients enrolled in the CLASSIC trial, Jayne *et al.*[41] reported that the rate of bladder dysfunction was similar between the open and laparoscopic surgery groups; however, the rate of erectile dysfunction was higher in the laparoscopic surgery group, which was attributed to the higher frequency of TME in the laparoscopic surgery group.

In their prospective randomized trial, Ng *et al.*[34] found that there was no significant difference in urinary or erectile dysfunction between the laparoscopic and open TME groups. In the COREAN trial, however, there were significantly fewer urinary complications in the laparoscopic surgery group[39]. Relatedly, McGlone *et al.*[53] compared patients undergoing proctectomy by laparoscopic and open surgeries. Urinary and sexual dysfunction was observed in both surgery groups; however, penetration success in males and sexual activity results in women were found to be better in the laparoscopy group.

Overall, the results of these studies indicate that there was no major difference in urinary or sexual dysfunction between patients undergoing laparoscopic and open rectal surgery and that the main causes of these complications were rectal resection and TME, not the surgical approaches.

DISCUSSION

The development of minimally invasive colorectal surgery has been the greatest technological advance in colorectal surgery in the past 20 years, with established benefits in short-term outcomes and return to function. Laparoscopic rectal surgery can promote patient recovery, overall outcome, and quality of life. Appropriate training is essential to achieve results that are at least comparable with oncological results. Most importantly, the concerns and controversies regarding oncological outcomes with laparoscopic TME should be resolved with the publication of the results of the studies evaluating long-term survival with this surgical approach.

CONCLUSION

TME, which should be performed to preserve the nerves and ureters, is technically difficult to perform in the pelvis. The surrounding tissues can be visualized more clearly with the laparoscopic approach; however, the angulation of the laparoscopic instruments and endoscopic staples is limited. Therefore, at least 50 laparoscopic rectal surgeries must be performed to achieve proper experience with this technique. The results of the studies published to date reveal that there is no difference in short-term outcomes between the laparoscopic and open approach. The long-term results of the limited number of trials conducted to date reported that the outcomes were similar between the two surgical groups; however, concerns remain regarding the utility of laparoscopy in locally advanced and distal rectal cancer, which should be addressed by evaluating long-term outcomes with additional randomized controlled trials.

DECLARATIONS

Authors' contributions

Both authors contributed to the conception and the design of the review.

Availability of data and materials

Not applicable.

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Conflict 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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Mini-invasive Surgery

Review

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Current state of transanal minimally invasive surgery in the management of rectal cancer

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Abstract

Rectal cancer surgery has undergone a rapid change over the last few decades. We have come a long way from abdominoperineal resection to minimally invasive sphincter preserving techniques. Colorectal cancer screening programs made it possible to diagnose patients at earlier stages and this has led to question the necessity of radical surgery and the possibility of organ preservation. The platform most recently added to the surgical armamentarium is transanal minimally invasive surgery (TAMIS). It utilizes conventional laparoscopic tools to perform endoluminal surgery in rectum. Along with the conceptual changes in rectal cancer management, TAMIS is more frequently used for local excision of malignant rectal tumors. This review highlights the recent advances and current state of the role of TAMIS in the management of rectal cancer at various stages.

Keywords: Rectal cancer, transanal minimally invasive surgery, local excision

INTRODUCTION

The ultimate aim of rectal cancer treatment is to provide safe oncological cure while maintaining enteral continuity and preserving sphincter function. In many cases, it is challenging to achieve excellent results in all three components[1].

The multimodal treatment of rectal cancer is following a similar path to breast cancer: less invasive surgical techniques are being utilized to preserve anatomical and functional integrity without compromising oncological outcomes. It has undergone a seismic change from abdominoperineal resection to low anterior resection, local excision and finally watch-and-wait approach, following neoadjuvant treatment in select patients. This change was manifest in tandem to the technical advancements like the introduction of circular staplers, surgical refinements - popularization of strict adherence to anatomical planes by Heald, and of course recognition of the importance of neoadjuvant chemotherapy and radiotherapy[2].

Not only has the nomenclature around the operation changed, but so too has the platform to access the rectum. The introduction of laparoscopy has revolutionised colorectal surgical practice and continues to evolve. Robotic surgery platforms have also garnered some popularity, in particular, for access to the lower third of the rectum. Since 2010, the introduction of minimally invasive approaches has been applied to the rectum via a transanal approach[3], and has been utilised in a broad spectrum of clinical scenarios; from transanal polyp excision to anastomotic leak repair, local excision of rectal cancer, transanal total mesorectal excision (taTME) and pelvic exenteration[4-9].

The advent of widespread colorectal cancer screening has made it possible to diagnose rectal polyps and early stage rectal cancers more frequently. This increasing trend along with increasing response rates to more effective neoadjuvant treatment for locally advanced rectal cancers and patient demands for organ-sparing options has led leaders in the field to push the boundaries of surgical approaches to the rectum and to reappraise the paradigm of formal proctectomy. Moreover, patients who require local palliation in the setting of stage IV disease and the aging population with medical comorbidities who would be otherwise unfit for any abdominal approach, constitute another group of patients for whom local interventions per anus may prove to be more beneficial overall.

The aim of this study is to review the current state of the role of transanal minimally invasive surgery (TAMIS) in the local management of rectal cancer and highlight the recent advances, with an emphasis on functional results and complications.

LOCAL EXCISION

The term "local excision" refers to removal of the tumor with negative surgical margins without removing the organ it originates from - the rectum. It involves full thickness resection of the rectal wall but not necessarily the draining lymphatics. Enthusiasm about local excision for early stage rectal cancer has grown after Morson *et al*.[10] published their results in 1977. This has led to development of techniques other than transanal excision (TAE), which is limited by poor exposure and limited to lesions in the distal rectum. Currently, the two most popular options for local excision are transanal endoscopic microsurgery (TEM) and TAMIS.

TAE utilizes conventional instruments under direct vision. It cannot reach mid- or upper rectal lesions. Moreover, confinement of the operative field risks the achievement of negative surgical margins. Margin positivity exceeds 10% even in experienced hands[11,12]. In a recent study, TAE is not considered as a feasible technique for tumors located higher than the first rectal valve, > 3 cm in size and deeper than T1[13].

TEM, first described in 1984 by Buess *et al*.[14] utilized a rigid platform to access intraluminal lesions in the rectum. It has several advantages over TAE. It maintains a stable pneumorectum and makes it possible to reach the mid and upper rectum. Improved visualization results in better assessment of resection margins. When compared to conventional TAE, TEM provides a superior quality resection, with higher rates of negative microscopic margins, reduced rates of specimen fragmentation and lesion recurrence, but with equivalent post-operative complications[15].

However, several factors have limited the widespread uptake within the armamentarium of colorectal surgeons throughout the world. These include a steep learning curve, significant cost of the operating system and concerns about postoperative function[16].

The need for an oncologically safe and also cost effective procedure led to evolution of TAMIS. TAMIS utilizes conventional laparoscopic devices and a single incision port rather than a specialized platform. Therefore, it lowers the cost of the procedure, while giving the surgeon an opportunity to operate with familiar instruments. It also allows for a 360° exposure of the rectal lumen, which is another superiority over TEM. While TEM requires repositioning of the patient or the platform, TAMIS allows operating in multiple quadrants using the same configuration. First described in 2010, TAMIS was found to be a feasible alternative to TEM, providing its benefits at a fraction of the cost without specialized instrumentation[1,3,17-19].

AN INDIVIDUALIZED APPROACH FOR PATIENTS

Patients with rectal cancer being considered for local excision, should undergo routine staging workup like any other rectal cancer patient, including dedicated magnetic resonance imaging of rectum for local staging, computed tomography of chest, abdomen and pelvis to screen for distant metastases and baseline carcinoembryonic antigen level to guide future follow-up and treatment.

Neoadjuvant treatment followed by TME is still considered the gold standard treatment for locally invasive rectal cancer in terms of oncological outcomes. However, it also has significant effects on patients' quality of life. The Dutch Colorectal Cancer Group reported 14% fecal incontinence, 52% bowel dysfunction and 57% urinary incontinence at 5-year follow-up[20]. These relatively high morbidity rates have strengthened the search for alternative treatment options providing a balance of favourable functional outcomes without compromising oncological results.

The uptake of colorectal cancer screening has enabled more patients to be diagnosed at an early stage[2]. We have also more knowledge about tumor biology and risk factors for aggressive behaviour of the disease. All of these together, bring up the potential for less radical organ preserving surgery in an effort to improve patients' quality of life. One concern for local excision is excessive tissue removal leading to a narrowed lumen and rectal stenosis. However, we know from TEM literature that stenosis following TEM excision is rare unless the lesion is circumferential. Recently, McLemore *et al.*[21] reported a single case of rectal stenosis in a cohort of 32 patients who underwent TAMIS for both benign and malignant rectal tumors. The patient who developed stenosis had a large circumferential adenoma and was subsequently managed successfully with endoscopic dilation.

T1N0

Early rectal cancer is defined as cancer confined to submucosa[22]. Kikuchi *et al.*[23] further classified early rectal cancer according to depth of invasion of the tumor by dividing submucosal layer into thirds. While the risk of lymph node metastasis is 3% for lesions invading the superficial 1/3 of submucosa (SM1), it rises up to 8% for middle (SM2) and to 23% for deeply invading lesions (SM3)[24-26].

The 2013 American Society of Colon and Rectal Surgeons practice parameters for the management of rectal cancer state that local excision is an appropriate treatment modality for carefully selected T1 rectal cancers without high-risk features[27].

Favourable T1 lesions have a less than 10% risk of lymph node metastasis and local excision can be potentially curable for these patients[2] [Figures 1-3]. The Swedish Rectal Cancer Registry analysis demonstrated that the rate of lymph node metastasis is 6% in the absence of adverse features (lymphovascular invasion or poor differentiation).

A recent analysis of Surveillance, Epidemiology, and End Results database, showed that local excision of T1 rectal cancer does not affect cancer-specific survival when compared to radical surgery. However, less radical approach comes at a cost of need for more frequent and careful follow-ups[28].

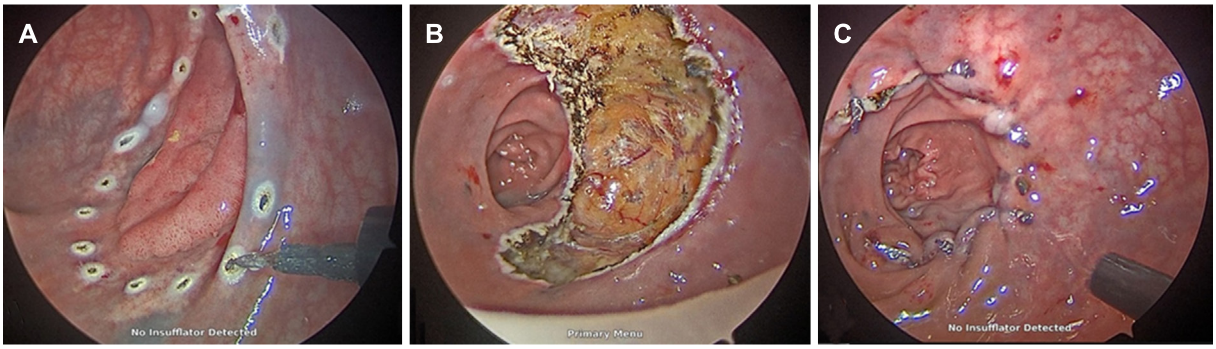

Figure 1. A T1 SM1 tumor excised by transanal minimally invasive surgery. A: Marking of resection margins with electrocautery; B: completed full thickness excision; C: closure of rectal wall defect

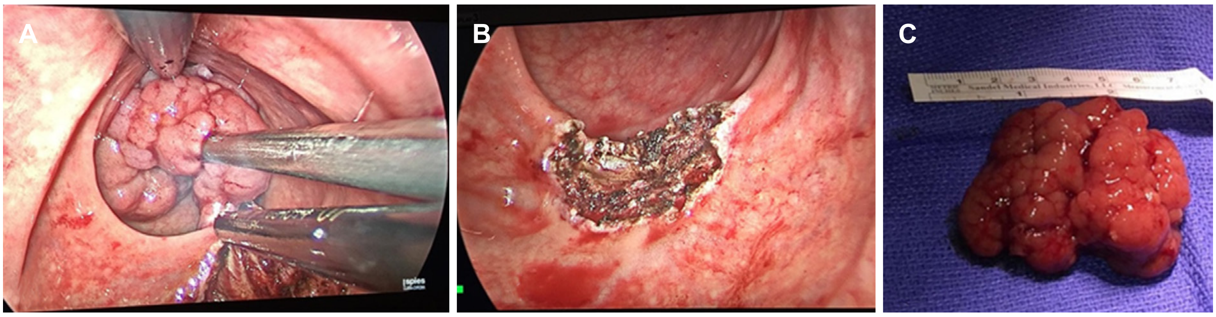

Figure 2. A near-obstructing T1 malignant polyp with a thin stalk excised by transanal minimally invasive surgery. A: Large tumor in mid rectum; B: rectal wall defect not closed after excision; C: the specimen after excision

Due to the fact that TAMIS is a novel technique, oncological outcome data after TAMIS for rectal cancer is limited thus far simply by length of follow-up. In a comparative study by Lee *et al*.[29], margin positivity was 7% and lesion fragmentation was 4% for TAMIS, which was not significantly different from TEM. Local recurrence was 6% after high quality excision compared with 13% after poor quality excision. Another study comprising 110 rectal cancer patients, a positive margin was seen in 8% and tumor fragmentation in 5% of patients. For patients who did not undergo immediate salvage radical surgery, local recurrence rate was 6%, and distant metastasis rate was 2% after a median follow-up 14.4 months[30]. Martin-Perez *et al*.[31] performed a systemic review of 16 high quality case series, they reported an overall margin positivity of 4.4% and tumor fragmentation was 4.1%.

On the other hand, another meta-analysis of 4510 patients highlighted the risk factors for lymph node metastasis for T1 lesions as submucosal invasion > 1 mm, lymphovascular invasion, poor differentiation and tumor budding[32]. If any of these risk factors are present on final pathology, total mesorectal excision is recommended in medically fit patients due to the high risk of lymph node metastasis. Similarly, for rectal neuroendocrine tumors > 20 mm or with adverse features, radical surgery is warranted in suitable patients[1,15]. Data from TEM literature suggest a reduction in mesorectal excision quality in patients who undergo salvage radical resection after local recurrence following local excision[33]. Lower quality mesorectal excision leads to higher local recurrence and a reduction in survival, which therefore emphasizes the importance of patient selection for local excision in the first place.

Local excision following neoadjuvant therapy

With increasing interest in watch-and-wait approach for complete clinical response following neoadjuvant chemoradiation, there has also been a trend towards local excision to evaluate and confirm mural pathologic response. Additionally, local excision is being utilized more commonly for patients whose tumors

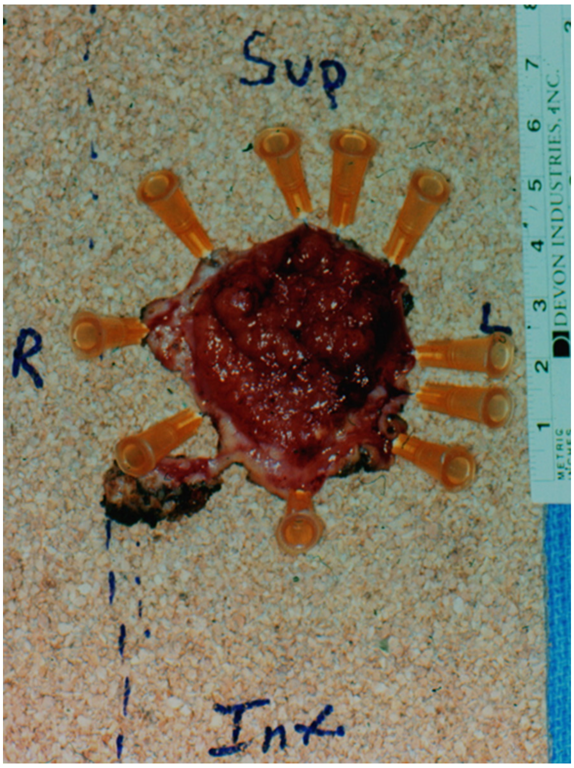

Figure 3. A T1 tumor excised with clear margins fixed on the board after transanal minimally invasive surgery excision

have been clinically downstaged but not responded completely. However it should be kept in mind that even with a complete pathologic response of primary tumor (ypT0), the risk of nodal positivity remains 3%-6%[34-36].

In 2016, Shin *et al.*[37] published retrospective data of 34 patients who had local excision following neoadjuvant chemoradiation. They included patients with only complete or near complete clinical response. A pathologic complete response was achieved in 56% of patients, 35% had T1 and 9% had T2 tumor in their final pathology. Only 2 patients developed recurrence (one local recurrence and one distant metastasis) during a 5-year follow-up period. In this study, all lesions were located in low rectum; 28 patients had TAE and 6 patients had TAMIS.

Lee *et al.*[30] published a wider range of patients with more advanced stage. They investigated the role of TAMIS for patients with T2/T3 N+ disease who received neoadjuvant chemoradiation and responded clinically with negative lymph nodes on post treatment imaging and a final tumor showing a small whitish scar and/or shallow ulcer on sigmoidoscopy. On final pathology, 18 patients showed a pathologic complete clinical response of primary tumor, whereas 11 patients still had T2/T3 tumor. All of these patients refused to undergo further surgery and nearly half of them (5 of 11 patients) developed local and/or distant recurrence during the median follow-up of 36 months.

Local excision for more advanced tumors

As of today, the gold standard treatment of T2-T4 lesions is TME due to high risk of lymph node metastasis. Local excision of T2-T4 lesions can be considered as an oncologically inferior but less invasive alternative to radical excision in several clinical scenarios; including patients with multiple comorbidities who are medically unfit to undergo a major abdominopelvic procedure or patients with metastatic disease but who need local control for palliation [Figure 4]. There may also be some patients who demonstrate understand-

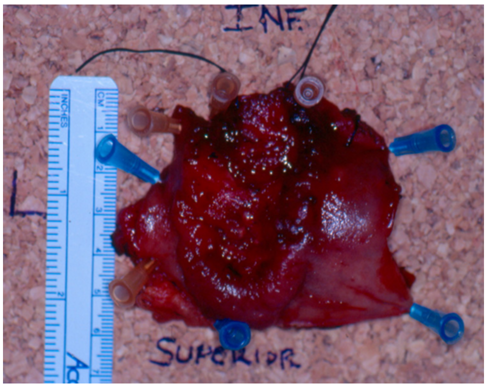

Figure 4. An obstructing T3 tumor excised by transanal minimally invasive surgery for palliation in a patient with liver and lung metastases

ing and refuse radical resection to avoid its complications like fecal or sexual dysfunction, or to maintain intestinal continuity and avoid a permanent colostomy with an acceptable risk of higher recurrence rate.

Knowledge about the role of local excision for lesions deeper than T1 is mostly limited to small series of patients who declined TME or were unfit for abdominal surgery[19] [Figure 5]. These series have reported significantly higher local recurrence rates. These series also do not follow a standard protocol of chemotherapy or radiotherapy.

Lezoche *et al.*[38] studied the long-term outcomes of 70 patients with T2N0 rectal cancer randomized to TEM or laparoscopic TME. All patients in each group had received neoadjuvant chemoradiation. They reported a local recurrence rate of 5.7% after local excision versus 2.8% percent after laparoscopic TME, with a median follow-up of 84 months. There was no difference in disease-free survival.

Similarly, American College of Surgeons Oncology Group (ACOSOG) Z6041 trial investigated the role of local excision for clinically staged T2N0 rectal cancer following neoadjuvant chemoradiation. Local recurrence rate was reported as 4% and distant metastasis as 6% after a median follow-up of 56 months[39].

FUNCTIONAL OUTCOMES AND QUALITY OF LIFE

The biggest driving force behind less invasive approaches for rectal cancer - especially for early rectal cancer - is the high morbidity of gold standard technique; TME. Functionally unfavourable outcomes in intestinal, urinary and sexual functions are the major concerns for patients' postoperative quality of life (QoL). Local excision can potentially decrease the incidence of these complications and improve QoL. TEM has been associated with fecal incontinence due to its 4-cm diameter scope and rates of up to 37% worse incontinence has been reported after TEM[40]. TAMIS seems more advantageous in this regard as it utilizes a flexible port to access rectum. Although longer term follow-up data is available for TEM, the impact of TAMIS on patients' QoL is unclear - due to it being a relatively new technique.

Recently, Clermonts *et al.*[41] published their data of 37 patients who underwent TAMIS for dysplastic sessile polyps or cT1 rectal cancer. They compared Short-Form 36 Health Survey responses of 37 patients to a healthy case-matched population. This study demonstrated that patients scored worse than healthy control group in physical functioning, general health perception and social functioning domains. After a 3-year follow-up, 9 patients reported improved fecal incontinence severity index (FISI) scores, 19 patients deteriorated and 9 patients remained same.

On the other hand, Verseveld *et al.*[42] compared QoL of 24 patients undergoing TAMIS before and 6

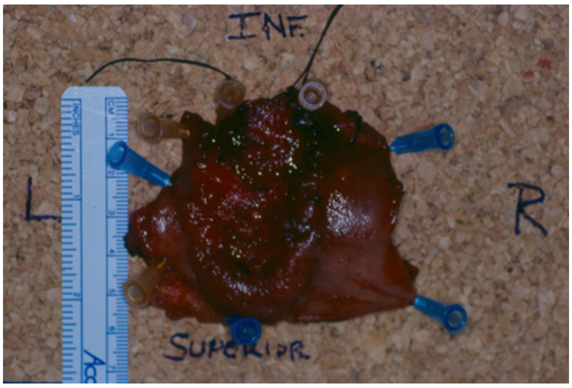

Figure 5. A T2 rectal tumor specimen fixed on board after transanal minimally invasive surgery excision

months after the surgery. They did not note any deterioration, but a general improvement in QoL and more specifically in FISI scores after TAMIS.

Schiphorst *et al.*[43] similarly reported FISI scores of 35 patients pre- and post-TAMIS. Their data showed that 3 of 18 patients with normal continence developed soiling after the surgery but 2 of them returned to normal in 6 months. Fifteen of 17 patients with abnormal FISI score showed improvement in fecal continence following TAMIS.

These studies yield varying results. It should be kept in mind that one of these studies compared TAMIS patients to healthy control group, and the other two compared the same patients' pre- and post-operative status. A study comparing functional outcomes and QoL of patients who underwent TAMIS versus TME would give a more meaningful picture in terms of the functional benefits of local excision over radical resection.

COMPLICATIONS

Lee *et al.*[29] reported postoperative morbidity of TAMIS to be 9% in a series of 228 patients comprising both benign and malignant tumors. In another study by the same group, complication rates of TAMIS in a group of 110 rectal cancer patients was 15%. The most common complications of TAMIS were urinary retention, perioperative bleeding and peritoneal violation; similar to TAE and TEM[30].

Both urinary retention and peritoneal entry have been associated with anterior and lateral location of the tumor. Urinary retention is usually self-limited and treated by temporary urinary catheterization. Entry into peritoneal cavity has been reported more frequently with upper lesion location (> 8-10 cm from anal verge). The largest TAMIS series published to date had an incidence of peritoneal entry of only 2%. In contrast, the incidence is reported as 6%-8.6% for TEM. Either transanal or laparoscopic suturing can be utilized when a peritoneal defect occurs. It is not associated with increased morbidity. Risk is further reduced in the setting of preoperative bowel preparation and intravenous antibiotic treatment for 24 h postoperatively[18,19,44]. In these patients, a gastrograffin enema is recommended on postoperative day 3 to document the absence of a leak[2].

Mean blood loss for local excision of rectal cancer is 28 mL[30]. Increased bleeding has been associated with large tumor size. Cases of post-procedural hemorrhage that do not stop spontaneously have in all cases been managed successfully either endoscopically or with examination under anesthesia and sewing[1].

Less commonly reported complications include urinary tract infection, subcutaneous emphysema, scrotal edema and hemorrhoidal thrombosis[2].

Barendse *et al*.[45] concluded that a learning curve effect was observed in complication rates. However, a specific case volume was not defined in this study and complication rates before and after the learning curve were not compared. Lee *et al*.[46] investigated the learning curve in a single high volume tertiary care referral center and found that the learning curve of TAMIS for rectal neoplasms is 14-24 cases. This study did not show a difference in complication rates before and after the learning curve.

CONCLUSION

Based on currently available clinical data, TAMIS in experienced hands, results in the high quality local excision of early rectal tumors with low histological margin positivity in an efficient manner and low recurrence rates in context of favourable histologic properties with an excellent morbidity profile with no long term adverse effect on continence. The role of TAMIS for more advanced tumors and in the post-neoadjuvant setting needs clarification by further studies. It can also be offered as a palliative procedure to patients with metastatic disease, which would potentially avoid complications of a major surgery. TAMIS has enabled the performance of high quality local excision of rectal lesions by many colorectal surgeons, integrating transanal endoscopic surgery into mainstream practice. Currently surgeon preference and device availability govern which platform is selected for use. As with all new techniques used in the management of neoplastic disease, appropriate training must be ensured and the continued assessment and assurance of oncological outcome - via databases - must be maintained.

DECLARATIONS

Authors' contributions

Design, literature research, manuscript writing, manuscript editing, manuscript revision: Erkan A, Kelly JJ, Monson JRT

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Mini-invasive Surgery

Review

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Reduced-port surgery for rectal cancer

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Abstract

Laparoscopic surgery for rectal cancer has short-term and long-term oncological outcomes similar to those of open surgery. Conventional multiport laparoscopic surgery (CMLS) for rectal cancer requires four or five abdominal incisions for trocars, each of which could lead to complications and/or pain. Single-incision laparoscopic surgery (SILS) would reduce the incidence of such wound-related complications and achieve better cosmetic outcomes relative to CMLS. The potential advantages of SILS are less pain and more rapid recovery than achieved with CMLS. However, SILS is rarely used for rectal cancer because of the high-level technical expertise required. Reduced-port laparoscopic surgery (RPS), which involves one additional port, may bridge the technical gap between CMLS and SILS and has a less steep learning curve. RPS for rectal cancer has a short history, and its usefulness has not yet been fully established. Here, we review the present situation, challenges, and future prospects for RPS for rectal cancer.

Keywords: Laparoscopic surgery, rectal cancer, reduced port surgery

INTRODUCTION

Large randomized trials [Conventional versus laparoscopic-assisted surgery in colorectal cancer (CLASICC), Clinical Outcomes of Surgical Therapy (COST), Barcelona, JCOG0404] and a meta-analysis have demonstrated that laparoscopic surgery for colon cancer is not only safe, but also associated with better short-term outcomes, with no negative effect on long-term survival[1-5]. They also revealed trends toward reduced postoperative morbidity, intraoperative blood loss, and pain, as well as faster recovery and better quality of life for laparoscopic surgery compared with open surgery[1,4,6-9]. The disadvantages were a longer operating time, higher theater costs, and a steep learning curve. However, the long-term recurrence rate was similar and no significant difference was found in the disease-free survival (DFS) or overall survival (OS) rate[4]. Therefore, laparoscopic surgery is now considered to be an acceptable approach for colon cancer.

However, some controversy surrounds the non-inferiority of laparoscopic surgery to open surgery for rectal cancer in terms of long-term outcomes. Two previous large randomized controlled trials (RCTs), the Colorectal Cancer Laparoscopic or Open Resection (COLOR) II and Comparison of Open versus laparoscopic surgery for mid or low Rectal cancer After Neoadjuvant chemoradiotherapy (COREAN) trials, and several meta-analyses showed similar pathological and oncological outcomes of laparoscopic and open approaches for rectal cancer, and the laparoscopic approach is now a standard alternative to the open approach[5,10-13]. However, two more recent RCTs, the ALaCaRT and ACOSOG Z6051 trials, yielded contradictory results, and failed to show the non-inferiority of laparoscopic to open rectal resection[14,15]. The most recent meta-analysis showed that the risk of a positive circumferential resection margin in rectal cancer was significantly greater for laparoscopic than for open surgery[16]. Although laparoscopic surgery might be useful for the treatment of rectal cancer in selected patients, the evaluation of long-term outcomes is needed to determine whether the poor pathological outcomes have adverse effects on DFS or OS.

Laparoscopic procedures are becoming less invasive. Conventional multiport laparoscopic surgery (CMLS) for colorectal cancer (CRC) requires four or five abdominal incisions for trocars, and each incision could be associated with wound complications and pain[17]. Single-incision laparoscopic surgery (SILS) would reduce the incidence of such wound-related complications and achieve better cosmetic outcomes relative to CMLS. The potential advantages of SILS over CMLS are less pain and early recovery. Indeed, SILS reportedly has more acceptable short-term outcomes compared with CMLS[18-21]. In addition, it has been reported that SILS performed by experienced laparoscopic surgeons for selected patients can be an oncologically safe option[22-24]. However, SILS is a highly demanding procedure with several technical challenges, such as the handling of conventional laparoscopic instruments through small incisions, which could decrease the range of motion, and the potential for collisions between instruments and the camera. As a result, SILS also has disadvantages, such as a longer operation time, increased surgeon fatigue, and a steep learning curve. Reduced-port laparoscopic surgery (RPS), which is single-port surgery with one additional port, may overcome the limitations of SILS while retaining its advantages.

Here, we review the present situation, challenges, and future prospects of the use of RPS for CRC.

A comprehensive literature search was performed following an electronic search of PubMed@. Articles published in the English language between January 2013 and June 2018 were evaluated using the key terms “RPS, CRC” or “SILS, CRC”. Case reports or small case series (< 20 cases) were excluded.

CMLS, SILS, AND RPS PROCEDURES FOR RECTAL CANCER CMLS

CMLS for CRC is usually performed via the five-port method, with an umbilical camera port, two operator ports, and two assistant ports[25] [Figure 1A]. The left colon is initially mobilized laterally to medially to the extent required for identification of the left ureter and left hypogastric nerve plexus. Mobilization of splenic flexure is performed if necessary. After intracorporeal high ligation of the inferior mesenteric vessels, mobilization of the rectum and mesorectum is performed. After mobilization of the rectum, a 3-4 cm abdominal-wall incision is made to extract the specimen. Bowel anastomosis is performed intracorporeally for anterior resection using a double-stapling technique.

SILS and RPS

A vertical 3 cm incision is made in the umbilicus and a multiple-instrument access port (MIAP) is placed

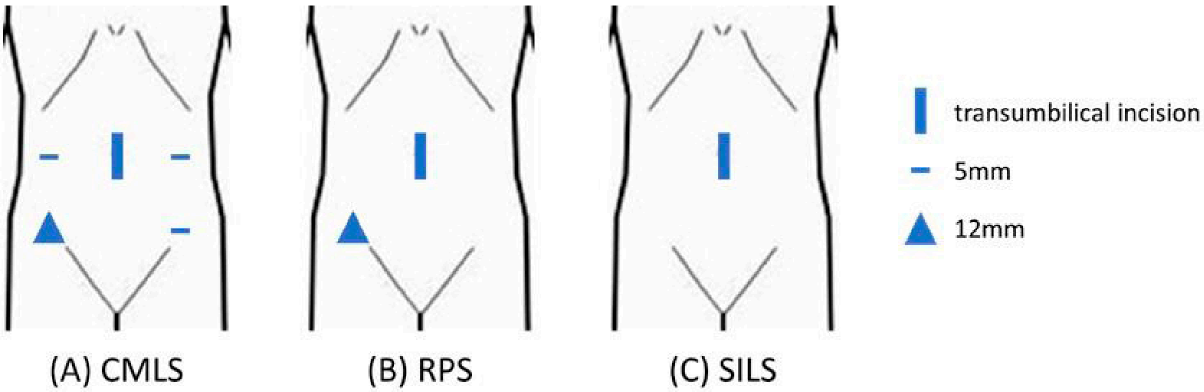

Figure 1. Trocars placement in conventional (A), reduced port (B) and single incision (C) laparoscopic surgery for rectal cancer

at the site[26]. SILS is performed entirely through this access port[27]. For RPS, an additional port is inserted on the operator's dominant-hand side [Figure 1A and C]. The assistant uses one channel of the MIAP to create a working view, and a 5 mm flexible-tip laparoscope is inserted through the other MIAP channel. A flexible laparoscope is useful for preventing interference from the hand instruments. After mobilization of the rectum, the transumbilical site is used to extract the specimen, and bowel anastomosis is performed in the same manner as in CMLS.

SILS compared with CMLS

Although no RCT on the subject has been performed, the most recent systematic review showed that colorectal SILS is at least as feasible and safe as CMLS in selected patients with rectal cancer[17]. SILS had outcomes comparable to those of CMLS in terms of operating time, conversion rate, reoperation rate, postoperative complication rate, and mortality rate. The oncological results of SILS for CRC were satisfactory, as demonstrated by similar average lymph-node retrieval and adequate resection margins relative to those obtained with CMLS. Nevertheless, long-term follow-up data on survival and local recurrence rates are lacking. In addition, colorectal SILS is technically limited because of instrument crowding, in-line viewing, and insufficient countertraction[24,28]. In particular, cutting of the distal rectum from the umbilicus using a linear stapler is technically difficult[29]. Therefore, the authors of the systemic review concluded that they could not recommend the use of SILS instead of CMLS for CRC[17].

RPS compared with CMLS

RPS has become more feasible due to the accumulation of experience and improvement of laparoscopic tools, such as energy devices and specific forceps. Although they included relatively few patients with rectal cancer, four retrospective studies have compared RPS with CMLS for the treatment of this disease[27,30-32]. The advantages of RPS over CMLS are summarized in Table 1. No RCT, systematic review, or meta-analysis has compared the outcomes of RPS and CMLS. An RCT of the short-term surgical and long-term oncological safety of RPS compared with CMLS for rectosigmoid colon cancer is underway[33].

One study evaluated long-term oncological outcomes after RPS for rectosigmoid cancer. Liu *et al.*[27] reported that the 3-year DFS and OS rates were comparable between the RPS and CMLS groups.

Regarding short-term outcomes, the operation time is shorter for RPS than for CMLS[27,30,31], possibly due to selection bias[30,31] or a decreased time to wound closure as a result of the fewer and smaller wounds created during RPS[30].

RPS is less invasive than CMLS and results in shorter times to flatus passage, liquid diet consumption, and

Table 1. Retrospective studies comparing reduced port laparoscopic surgery and conventional multiport laparoscopic surgery (CMLS) for colorectal cancer (CRC)

Author	Publication year	Reference	Total patients included (RPS *vs.* CMLS)	Accrual	Difference seen in RPS	
Kang *et al.*	2018	31	73 *vs.* 111	2011-2017	Operation time	Shorter
					Gas passage time	Longer
Song *et al.*	2016	32	32 *vs.* 217*	2011-2013	Operation time	Shorter
					Blood loss	Less
					Gas passage time	Shorter
					Pain	Less
Liu *et al.*	2017	27	48 *vs.* 48**	2011-2014	3Y DFS	N.S.
					3Y OS	N.S.
					Operation time	Shorter
					Total incision length	Shorter
					Time to liquid diet	Shorter
					Time to ambulation	Shorter
					Discharge	Less
					Pain	Less
					Postoperative CRP and IL-6 levels	Lower
					Cosmesis	Better
Kawamata *et al.*	2014	33	20 *vs.* 20	2010-2012	Operation time	N.S.
					Postoperative neutrophil counts	Lower
					Postoperative body temparature	Lower

RPS: Reduced-port laparoscopic surgery

ambulation[27,31]. In addition, RPS leads to less postoperative pain and better cosmetic results than does CMLS because of the shorter total incision length[27,31]. Therefore, patients who undergo RPS have better postoperative outcomes. However, the estimated blood loss, morbidity rate, conversion rate, and number of harvested lymph nodes were comparable, suggesting that RPS is a feasible and safe procedure in the early postoperative stage[27,30]. Furthermore, the postoperative neutrophil count, C-reactive protein level, interleukin-6 level, and body temperature were significantly lower after RPS compared with CMLS[27,32], which may accelerate recovery. Another advantage of RPS may be its cost effectiveness. The instrument cost for RPS may be lower due to the reduced number of trocars required; however, previous studies have not evaluated this factor. A shortened hospital stay and decreased analgesic use may also reduce the cost[34,35].

A MIAP can be placed at the ileostomy site and the excised specimen can be brought out during a reduced port laparoscopic low anterior resection with diverting ileostomy. Furthermore, a drainage tube can be placed via the additional port[36]. The use of MIAP as the ileostomy site represents a minimally invasive approach that results in a scarless procedure.

Superiority of RPS over SILS

RPS for CRC may have several advantages over CMLS. Since Burcher *et al.*[37] performed the first SILS for colorectal diseases, it has become widely used because of technical advancements. However, SILS has a risk of collisions between instruments and is limited by use of triangular tissue traction[21,24,38]; consequently, SILS is used infrequently worldwide[36]. In contrast, the additional port created during RPS reduces the risk of collision between surgical instruments and the laparoscope, as well as shortening the operation time compared with SILS[27]. Therefore, RPS involves fewer technical difficulties than does SILS. Moreover, RPS has other advantages over SILS, such as the convenience of an intracorporeal suture and stable drain placement via the additional port.

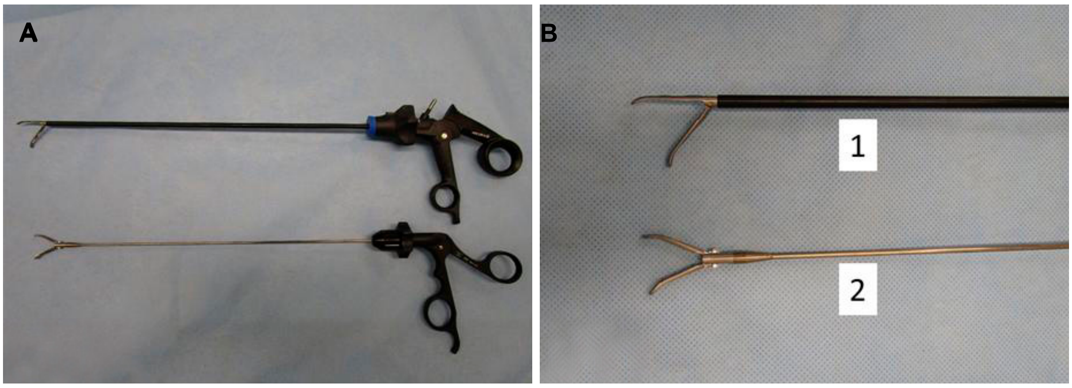

Figure 2. (A): Gross view of the instruments used in needlescopic surgery; (B): close up of the tips of the instruments shown in (A); 1: conventional 5 mm forceps; 2: same-sized tip section as that of the 5 mm forceps with a 2.4 mm-diameter shaft

SILS was initially expected to result in less postoperative pain compared with CMLS. However, this argument is controversial; indeed, the degree of postoperative pain after SILS is reportedly similar to or greater than that following CMLS[39-41]. Although SILS involves fewer incision sites, the single incision could be lengthened and stretched by insertion of a single port due to the challenges of handling conventional laparoscopic instruments[27]. This factor might explain the postoperative pain after SILS. The advantages of RPS are a reduced level of technical difficulty and cosmetic outcomes similar to those of SILS, and an operation time comparable to that of CMLS. In addition, the lengthening and stretching of the single incision are reduced during RPS relative to SILS, which may decrease postoperative pain. The results of a large prospective RCT comparing RPS with CMLS are awaited[33].

Future perspectives

RPS may be superior to SILS for CRC, as it has a lower level of technical difficulty while maintaining less invasiveness. However, RPS is typically performed by a single surgeon and a laparoscopist, and has a steep learning curve because the reduced number of ports interferes with forceps mobilization, leading to less effective countertraction and visualization. Therefore, RPS may still be difficult to perform for less experienced surgeons.

To overcome this difficulty, needlescopic surgery, which involves the use of forceps with a small-diameter shaft instead of the conventional 5 mm port, has been developed[42] [Figure 2]. Although the feasibility of needlescopic surgery compared with CMLS for CRC has been evaluated[43,44], needlescopic surgery is expected to be less invasive and produce better cosmetic outcomes than CMLS. In addition, needlescopic surgery for CRC does not increase surgeon stress, as it is basically identical to CMLS for all surgical procedures. The disadvantages of the use of a small-diameter shaft in needlescopic surgery are the low shaft stiffness and inability to exchange instruments[42]. However, the stiffness and operability of these tools have gradually been improved.

Although further prospective randomized studies of RPS (including needlescopic surgery) compared with CMLS for CRC are required, needlescopic surgery for CRC may be a good starting point for young surgeons and make feasible even less-invasive surgery.

CONCLUSION

Although further investigation is required, the surgical and oncological outcomes of SILS and RPS suggest that they are safe and feasible procedures. RPS may be superior to SILS due to its lower level of technical difficulty while maintaining less invasiveness.

DECLARATIONS

Author's contributions

Design, manuscript writing: Shigeta K, Ishida T
Literature research, data analysis: Ishida T
Manuscript editing: Okabayashi K, Tsuruta M, Hasegawa H, Kitagawa Y

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All authors declared that there were no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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Mini-invasive Surgery

Review

Open Access

Enhanced recovery after rectal surgery: what we have learned so far

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Abstract
Enhanced recovery after surgery (ERAS) protocols are gradually becoming the gold standard in the perioperative management of rectal patients. It is a multimodal and multidisciplinary approach that has the great merit to involve and empower the patient and bring him or her back to the centre of the strategy of care. If applied correctly, ERAS can improve the postoperative recovery, reduce the rate of complications and reduce the postoperative length of stay, in patients who had extensive pelvic dissection. The factors within ERAS and their application do not represent rigid schematizations but fluid concepts that may undergo substantial changes as soon as new evidence becomes available. The ERAS principles must be adapted to the specific environment and each team is expected to set up their own programme and quality control criteria. In this comprehensive review, the latest evidence and trend on enhanced recovery after rectal surgery have been critically appraised and presented.

Keywords: Laparoscopic surgery, rectal surgery, enhanced recovery after surgery

INTRODUCTION

The enhanced recovery after surgery (ERAS) programmes have been introduced in the 90s to improve the outcome of patients undergoing major surgery[1,2]. The concept at the basis of ERAS is to apply the best and most recent evidences of the literature to set up standardized perioperative protocols to improve the postoperative recovery and, only as an obvious consequence, to reduce the length of hospital stay (LOS)[3-5]. Unfortunately, the name initially used for these new protocols - "Fast Track" - sounded like a suggestion to discharge surgical patients too early and probably unsafely and many patients regarded it only as a way to reduce the costs for the hospital, without any benefit for them who, on the contrary, were exposed to serious risks at home for being discharged prematurely. At the same time, many doctors were concerned regarding the possible medico-legal risks, if complications occurred in patients after their early discharge.

On the contrary, the more recent and positive denomination of ERAS evokes a significant improvement of the experience of the patient undergoing major surgery. ERAS protocols aim at optimising the postoperative recovery as they "reduce surgical stress, maintain postoperative physiological function, and enhance mobilization after surgery"[6].

In fact, it has been demonstrated that elective patients treated with ER protocols recover better and quicker with respect to those treated under the traditional protocols. Time to first flatus, time to full oral intake and time to full mobilisation are reduced within an ERAS protocol with respect to the traditional postoperative care, and this leads to improvements in patient satisfaction and reduction of costs[4].

General morbidity and specific medical complication rates after surgery are reduced, although the rate of surgical complications doesn't seem to be affected[7-11]. On a physiological level, the control of insulin-resistance index and the reduction of the levels of cortisol and cytokines with respect to the "traditional" management demonstrate that ERAS yields a reduction of the postoperative stress response and hence the risk of complications[12].

As a consequence, postoperative LOS is reduced as well[12,13]. The UK national audit results published in 2015 confirmed that adherence to ERAS pathway is weakly but significantly associated with overall reduction of LOS. The weakness of this association may raise the hypothesis that it is more than single elements of ERAS acting directly on LOS and that ERAS as a whole, yields a mentality change that leads to better postoperative recovery[14], also in very elderly patients[15].

Instead of increasing the risk of complications, as initially feared, early discharge seems to be a protective factor towards complications[12]. Although we feel this may be considered an over optimistic message, it is obvious that discharging a patient early in their postoperative course would allow him or her to recover completely in their own environment, thus decreasing the risk of hospital-acquired infection and other complications linked to prolonged hospitalisation, including psychological issues.

Clearly, it is important that every system is in place to make sure that patients are adequately followed up at home in their early postoperative period, even if by phone only, and they have a clear pathway to access senior review if and when needed.

Furthermore, ERAS allows an early warning for eventual complications. In fact, a patient who does not recover as expected in the postoperative period - delayed recovery of their bowel function, altered vital signs and parameters, difficulty with mobilization - is likely to be developing a complication and this should prompt the early start of the diagnostic-therapeutic pathway to rule out or treat eventual complications. On the contrary, a patient who clinically recovers quickly and completely, whose bowel works normally (no need to wait a full bowel motion, but just the first flatus), his vital signs are normal and pain is easily controllable can be discharged very early (even on the same day if the safety network is in place) with very low risk of complications and readmission.

However, we would expect that a number of patients would develop complications after their discharge and might need to be readmitted. This does not represent a failure of the ERAS pathway, as the outcome of complicated and readmitted patients is not different from the outcome of complicated in-patients who did not need readmission[16].

ERAS is by its own nature a multidisciplinary approach, where the paradigm of surgical treatment has been shifted from the surgeon to the team, consisting of surgeons, anaesthetists, physiotherapists, dieticians, physician assistants and specialist nurses. Adherence to the protocols is crucial to get the positive effects of ERAS in terms of better recovery, fewer complications, reduced LOS, reduction of costs and increased patient satisfaction[17].

Although ERAS principles are gradually spreading to every surgical specialty, due to local or national arrangements, the initial and still greatest interest is in colorectal surgery[12]. Within this specific field, a further division has been done between colonic[6] and rectal[18] surgery. Although this differentiation sounds to us a bit forced - as any excessive subspecialisation - we cannot deny that some issues specific to rectal surgery still exist and will be highlighted in the present review. With respect to colonic surgery, extraperitoneal rectal surgery is often associated with higher risk of complications due to (1) critical blood supply to the rectal stump and the proximal colonic stump in anterior resection due to anatomical reasons; (2) more difficult surgical technique and longer operation time; (3) previous pelvic radiotherapy; and (4) more frequent need for covering stoma. For these reasons, postoperative length of stay is usually longer after rectal resection with respect to colonic resection.

The ER protocols have 3 fundamental steps: (1) preoperative; (2) intraoperative; and (3) postoperative [Figure 1]. This artificial division does not reflect into the reality, as the three components overlap and interlace very often and one influences the others.

PREOPERATIVE STAGE

The preoperative phase of the ERAS protocols is crucial for the success of the whole treatment. For this reason, the full potential of ERAS can be obtained only in elective patients, as those needing an emergency operation may miss this important step. To try and extend the benefits of ER also to patients admitted as emergencies, one of the Authors endorsed a staged approach in patients with acutely complicated colorectal cancer, with an initial damage control procedure followed by an elective resection after the patient has been stabilized and fully investigated and prepared[19].

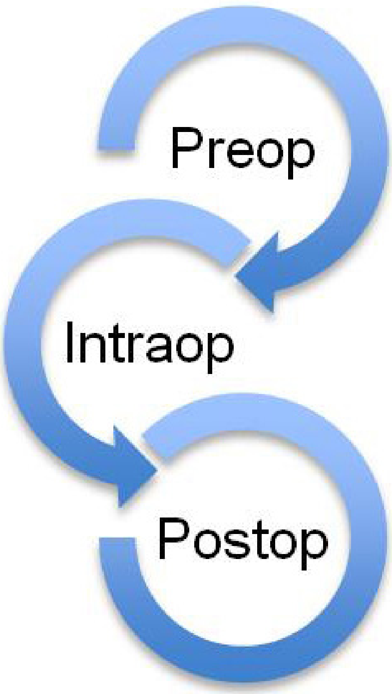
However, quite recently, emergency operations have been included into ER protocols, as it was felt that emergency patients can benefit from some of the improvements yielded by ERAS[20].

Preoperative counseling

One of the great advantages of ERAS is that the patient has been brought back to the centre of the whole experience and has been empowered to take care of him/herself and their recovery. The first meetings with the patient before their surgery are paramount to ensure the correct application of the ERAS protocol.

During the first encounters, after discussing diagnosis and treatment, the patient is offered to be included into the ERAS programme. Actually, the advantages of ERAS versus the traditional perioperative protocols have already been extensively demonstrated, so in our opinion there is no need to consider ERAS as a "special" measure and the ERAS principles must be considered at the basis of the standard and routine management of surgical patients. Placing special attention on ERAS - with specific paperwork - makes it appear as if it is still a sort of "experimental" treatment needing a "special" consent - which is clearly not the case.

It is true, however, that patients must be accurately informed before the operation, which is best practice anyway, of the kind of management they can expect before, during and after surgery. All the elements must be discussed, including bowel and systemic preparation, DVT and antibiotic prophylaxis, surgical



Preoperative counseling/stoma education
Optimization - pre-habilitation
Preoperative nutrition
Selective bowel preparation

No fluid overload
Antibiotic and DVT prophylaxis
Short-acting anaesthetic agents
Minimal use of opioids
Prevention of hypothermia
Mini-invasive technique
Selective use of drains, < 24 h
No nasogastric tube
Bladder catheter < 24 h

Multimodal postoperative analgesia
Ideally no morphine > 24 h
PONV prevention
Prevention of postoperative ileus
Early feeding
Early mobilization

Quality control/audit

Figure 1. ERAS flowchart

technique, postoperative diet, mobilization/rehabilitation and pain control. In particular, the discharge must be prepared well in advance, in the preoperative period, and all the systems must be put in place for a safe return home. Involvement of the patient and their family (not only providing information) is crucial. A recent non-blinded randomized controlled trial from Norway clearly showed the value of extensive counseling within an ERAS programme in colorectal surgery. Patients who received repeated information preoperatively showed a more efficient engagement in some elements of the ERAS programme such as early feeding and early mobilization after surgery, thus reducing their LOS by 2 days with respect to the patients who received only standard information[21].

In our practice, the patient has at least 3 important meetings before surgery: (1) with the consultant surgeon, who communicates the diagnosis, offers and discusses the treatment and introduces ERAS; (2) with the anaesthetist, who provides preoperative optimization of the patient, discusses the pre, intra and post-operative anaesthesiological management and explains the ERAS in more detail; and (3) with the colorectal nurse who is responsible for a holistic approach and oversees some particular elements of the ERAS protocol. Sometimes the colorectal specialist nurse can be in charge of the ERAS protocol as well as the preoperative stoma teaching and site marking. In fact, the creation of a stoma is itself a contributory factor of prolonged LOS, therefore with the ERAS protocol we should aim at reducing the impact of stomas on the postoperative recovery. Stoma education is more effective if initiated in the preoperative period[22]. It is mandatory that that criteria and pathway for discharge are discussed with the patient at this stage[23].

Optimization

During the preoperative meetings, all the comorbidities are fully investigated and the patient is optimized for surgery, including quitting smoking and alcohol, rebalancing their sugar levels and addressing their nutritional needs. Clearly, the optimization process needs time, and the ERAS Society guidelines suggest that preoperative counseling must take place 4 weeks before surgery[18].

Despite some less than enthusiastic report[24], pre-habilitation is becoming a key factor in increasing the functional capacity of the patient before an operation[25,26]. It has been defined as a multimodal protocol involving not only nutritional assessment and support, but also physical exercise. Typically, patients considered for prehabilitation are recruited in a 3 or 4-week supervised physical training associated with unsupervised home exercises. This schedule has been demonstrated to be beneficial to improve the cardiopulmonary exercise test scores[27,28] and to significantly reduce LOS and length of recovery[28,29]. The effect of prehabilitation as opposed to standard rehabilitation is more evident in sedentary people[30].

It is clear that this protocol is time-consuming and may delay curative surgery for cancer. In particular in the countries, such as the UK, where cancer targets exist and require the operation to be performed as soon as possible after the diagnosis, prehabilitation has not been diffusely accepted yet due to the fears that a prolonged preoperative interval would impair survival[31]. However, a recent prospective study from UK has demonstrated that time from diagnosis to surgery - either 4, 8 or 12 weeks - does not impact on survival, so the regulatory pathways can safely be changed to accommodate prehabilitation[32]. A few prospective trials are still ongoing and are targeted at assessing the value of physical prehabilitation in patients scheduled for colorectal surgery[28,33-35]. We are looking forward to evaluating their results. However, it should be universally clear by now that prehabilitation should be included in every ERAS protocol, possibly adding also anxiety-reduction techniques which may benefit both the psychological and physical wellbeing of patients undergoing major rectal surgery[36].

Preoperative nutrition

One of the new concepts highlighted by ERAS is that a correct preoperative nutrition can improve postoperative recovery by reducing the effects of surgical stress. As malnutrition is a negative prognostic factor for LOS and complications[37], nutritional assessment and support have been included in the prehabilitation programme.

It has been demonstrated that the traditional long fasting before the operation has no advantages in terms of possible risk of inhalation[38] and, on the contrary, can be detrimental due to the risk of increasing the physiologically stress-related insulin-resistance[39]. Randomized controlled trials demonstrated that the administration of a specific sugary fizzy drink before the operation could reduce postoperative insulin-resistance, other than hunger, thirst and anxiety[23]. The preoperative sugar load would improve the metabolism of proteins and nitrogen and reduces the detrimental catabolic effects of surgical stress on the muscular mass and the healing process[40,41], thus reducing the risk of complications and expediting the recovery.

Recent recommendation of the American Society of Anesthesiologists is that patients should have free access to fluids up to 2 h before surgery and to solid food up to 6 h before surgery, thus resembling a "normal" nutritional pattern[42]. Particular attention has been suggested - at least initially - to diabetic patients, where sugary drinks can potentially derange their glycaemia. Moreover, patients with complicated type 2 diabetes are known to have an increased risk of delayed gastric emptying, so - at least theoretically - the ERAS recommendations must be applied with special care.

Immuno-nutrition has been recently introduced as a way to reduce complications and improve recovery. The SONVI Study compared an immune-enhancing pre and postoperative nutrition with the traditional hyper caloric hypernitrogenous supplement within an ERAS programme and found that the number of infective complications was significantly reduced in the treated group[43]. Immuno-nutrition will be further discussed.

Nutritional supplements are mandatory in malnourished patients and preoperative enteral or parenteral feeding should be considered in patients who are not meeting the nutritional requirements.

Bowel preparation

Mechanical bowel preparation (MBP) has always been one of the cornerstones of colorectal surgery and lower gastrointestinal endoscopy, but it may be associated with dehydration and electrolyte imbalance, in particular in high risk patients (advanced age, renal impairment, liver failure). A Cochrane systematic review published in 2005 indicated that MBP does not prevent anastomotic complications and therefore should be avoided[6,44]. Although it was clear that this review was poorly significant due to high heterogeneity, it was suggested that no patient scheduled for colorectal resectional surgery should have his/her bowel prepared. A RCT trial published in 2010 and a new Cochrane review published in 2011 found that, although bowel preparation would make no difference in colonic surgery, it may be beneficial - and hence used selectively - in patients undergoing rectal surgery[45,46]. More recent studies seem to give contrasting results.

Two recent meta-analyses on this subject, one conducted in the USA and the other in Europe, propose a totally different approach. Yost *et al*.[47] from Massachusetts found that MBP associated with oral antibiotics can reduce the risk of anastomotic leak, wound infection and postoperative sepsis, and facilitate the manipulation of the bowel in laparoscopic surgery. On the contrary, the systematic review by Leenen *et al*.[48] from the Netherlands arrives to the conclusion that MBP does not decrease the incidence of leak, but admits that the study is flawed by the small size of the sample and the heterogeneity of the studies reviewed. Already in 2015 a retrospective study on prospectively collected outcome data from the National Surgical Quality Improvement Program on 8442 patients showed that MBP almost halves the risk of anastomotic leak, ileus and surgical site infection[49].

The different approach to this issue between the two sides of the ocean reflects in the official guidelines. The 2012 guidelines of the European ERAS Society clearly state, that MBP should be avoided in colonic and rectal surgery[6,18]. On the contrary, the 2017 ASCRS/SAGES guidelines advocate the use of MBP with oral antibiotics[23]. This difference can be explained, at least partially, by the fact that the US review took into account more recent evidences, clearly not available 5 years before, but also by the different cultural, and probably financial attitude. Although local guidelines must be developed and validated, it is undeniable that at the moment this is still matter for debate and a definitive answer is yet to come. We feel that with the current status of evidence the ultimate choice must stay with the consultant in charge, as some surgeons may feel more confident to operate on a completely empty and deflated bowel, mostly in laparoscopy, whereas others do not see the presence of a non-prepared bowel as a limitation or increasing difficulty. The role of oral antibiotics associated with MBP is gaining popularity after the studies of Alverdy and his team in Chicago[50] and the ERAS guidelines of the ASCRS/SAGES[23].

INTRAOPERATIVE STAGE

Intra and postoperative fluid therapy

The traditional liberal infusion of fluids during and after a major operation, either by open or laparoscopic surgery, has been demonstrated to be one of the causes of prolonged postoperative ileus, probably due to the tissue oedema or sodium excess, and other perioperative complications, therefore is has been suggested to have a more restrictive fluid regimen[51,52]. The so called "goal-directed fluid therapy" has been considered as the first choice to correctly titrate the amount of fluids to be infused during and after a surgical operation[53]. Invasive and non-invasive monitoring systems have been used to utilize cardiac output as a guide for fluid infusion[18,54], but currently most teams prefer to adopt a more "empiric" system, with a low volume of intraoperative infusions followed by free oral fluid in the immediate postoperative period, at least in elective patients with no important comorbidities. Obviously, cardiac output remains the best indicator of volaemia (and oxygen delivery), but pulse, blood pressure and urine output are generally considered good enough to guide fluid infusion in rectal surgery. The growing diffusion of laparoscopic surgery, which entails reduced evaporative fluid loss and reduced blood loss with respect to open surgery, has helped significantly to reduce the amount of volume to be infused. However, the recent RELIEF trial failed to demonstrate a higher rate of disability-free survival and pointed out an increased risk of acute renal failure in patients with restricted fluid infusion[55]. Although this interesting study is gradually contributing to switching the paradigm of restrictive fluid infusion, we can reasonably admit that at the moment the pathophysiology of fluid infusion during surgery is not yet completely understood and we may still decide case by case on empiric bases until more definitive evidence becomes available.

The vast majority of published articles do not differentiate between colonic and rectal surgery, but rectal surgery is more easily associated with dehydration or hypovolaemia due to increased duration of surgery, bowel preparation and possible blood loss in the pelvis, therefore a less restrictive fluid infusion may be advisable.

Our attitude is to reasonably limit the intraoperative infusion to maintain adequate tissue perfusion during the operation and to allow the patient to consume free or clear fluids as soon as he or she is awake and comfortable in the recovery room after surgery. Invasive monitoring of the cardiac dynamics increases the risks, delays the mobilization and raises the costs of surgery, but it may be necessary in selected cases, mostly in unprepared patients.

Antibiotic prophylaxis and DVT prophylaxis

It has been widely demonstrated that systemic antibiotic prophylaxis reduces the risk of postoperative infections[56]. Both ultra-short term prophylaxis (a single dose before surgery) and short term prophylaxis (a preoperative dose plus 24 h coverage after surgery) revealed effective. It is still a matter for debate what antibiotics should be used. Clearly, they must be active on aerobic and anaerobic so usually a combination of two antibiotics is needed, but the choice is usually left with local policies and protocols. The first dose should be administered within 1 h from skin incision. Apparently, the association of intravenous and oral antibiotic is more effective than intravenous alone[57]. Much debate has been done recently on the use of intraluminal antibiotics in association with mechanical bowel preparation (see dedicated paragraph), which would be able to reduce the risk of ileus and leak.

DVT prophylaxis has been one of the pivots of the traditional perioperative management for decades. It is well known that the correct administration of low-molecular-weight heparin and the use of thromboembolism deterrent stockings (TEDS) would decrease the risk of DVT and pulmonary embolism. Obviously, this best practice has been integrated into the ERAS protocols.

Anaesthesia

Open rectal surgery usually needs a long abdominal incision, a wide pelvic dissection and sometimes also a perineal incision with severe disruption of the pelvic floor. The laparoscopic approach reduces the trauma of the midline laparotomy, even if often a small laparotomy may still be needed, but increases the operative time and adds the further pathophysiologic trauma of a steep Trendelenburg position.

The ERAS principles pertaining to anaesthesia are: (1) short-acting agents to expedite the postoperative recovery; and (2) optimal pain control with minimal use of opioids. Intraoperative pain relief can be obtained with a blended approach with epidural analgesia (see postoperative analgesia) and short acting opioids. Remifentanyl can reduce the surgical trauma and the stress response. Muscle relaxation is essential in laparoscopic surgery of the pelvis - much more than in open surgery - to allow a complete distension of the abdomen without contrasting the CO_2 insufflation and to facilitate the pelvic dissection[23].

Prevention of hypothermia

It is well known that hypothermia is one of the killers of the surgical and trauma patient, also due to its negative effect on coagulation. It has been demonstrated, and is considered best practice, that prevention of hypothermia through the administration of warm fluids and the use of a thermic blanket can reduce bleeding, surgical site infection and cardiac complications.

Hypothermia can also be detrimental in terms of prolonging the admission and delaying oral feeding, but its direct relation with postoperative ileus has not been proved[58]. It has been suggested to monitor body temperature during and after surgery[18].

Surgical technique

The ERAS being mostly a perioperative policy, the surgical technique is pretty much unchanged with respect to the traditional protocols. However, if we want to get the whole range of benefits of ERAS, it is clear that the surgical technique must be as less invasive as possible. Therefore, the higher benefits of ERAS can be obtained in patients operated by laparoscopy[2,5]. Although pelvic dissection is always traumatic, in particular when coupled with perineal dissection, the laparoscopic approach associated with ERAS would reduce postoperative ileus and overall physiologic recovery[18]. Numerous and strong evidence[59,60] confirmed that laparoscopic surgery for rectal cancer is feasible, safe and effective and adds the benefits of the mini-invasive approach to the care of patients with rectal malignancies. The combination of laparoscopic surgery with the ERAS approach improves the already outstanding results of each of the two taken singularly; therefore we strongly believe that laparoscopic surgery must be considered one of the core items of ERAS also in pelvic benign and malignant conditions.

Use of drains

If one of the principles of the surgical technique under an ERAS protocol is to be respectful of the particular pathophysiology of the patient, it necessarily follows that all those items that can delay his or her recovery should be avoided. The presence of one or more drains in the pelvis can impair the patient's early mobilization, without reducing the incidence or the severity of anastomotic leaks[61,62]. A large retrospective study from Holland and a meta-analysis from Italy showed that in patients who had total mesorectal excision the use of drain can be beneficial[63,64], but this finding was not confirmed by the GRECCAR 5 randomized controlled trial[65].

Nasogastric tube

The traditional use of a nasogastric (NG) tube to prevent postoperative vomiting and gastric distension has been demonstrated to be detrimental to an expedited recovery as it may be one of the causes of respiratory complications. A Cochrane meta-analysis demonstrated that bowel motility recovers quickly without a NG tube, with no increased risk of inhalation[66]. NG tubes should be reserved to those patients who develop postoperative ileus[23].

Bladder catheter

The use of a bladder catheter (either transurethral or suprapubic) has been part of the traditional perioperative management for decades, as it allows to monitor the urinary output and to deflate the bladder to improve the visualization of the pelvis, either by open or laparoscopic surgery. Moreover, it can be useful if the patient is not yet fully mobile. In rectal surgery, bladder catheter is standard practice due to the risk of urinary function impairment. However, there is no evident advantage in maintaining the catheter beyond the strict necessity. Several studies, and consequently the ERAS guidelines, suggest taking it out as soon as possible, even within the 1st day[18,67]. The American guidelines differentiate colonic and rectal surgery and suggest removal of the bladder catheter within day 2 in infraperitoneal rectal resections. Obviously, a longer duration of bladder catheterization may be necessary in patients with increased risk of urinary retention[18], such as in the presence of epidural analgesia, and in those who had extensive pelvic surgery[23].

Prevention of postoperative infections

Colorectal surgery patients are more prone to develop infections than any other surgical patients, possibly due to the high potential for bacterial seeding and/or translocation. Whereas specific infective processes such as pneumonia have a clear pathophysiology, it is still not perfectly clear why patients develop surgical site infection (SSI). The traditional view that this may be due to direct contamination during the operation, suspected on the basis that the most common causative bacteria of SSI are enteric in origin (*E. coli*, B. fragilis), has been disproved by the fact that cultures of the wound at the end of a surgical operation are not predictive of postoperative infection[68]. It has been proposed a "Trojan Horse" hypothesis for SSI, whereby virulent bacteria normally quiescent within the gastrointestinal tract are simply transferred to the surgical wound by neutrophils and macrophages activated by the surgical trauma[69]. The use of oral non-absorbable antibiotic would therefore be beneficial also in reducing the risk of SSI[23,50].

A similar mechanism has been invoked for the genesis of anastomotic leak. It has been demonstrated long ago that bacteria and not technique are usually responsible for anastomotic leak[70]. Unfortunately, for some reasons the view that local ischaemia and technical failure are the main causative factor for leak prevailed, despite the clinical evidence that oral antibiotics would decrease the risk of leak[71], until the more recent evidences[49] convinced the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons to include oral antibiotics in their ERAS guidelines[23].

The adoption of a bundle of measures to reduce SSI is a winning entry. A recent systematic review and meta-analysis showed a reduction of the risk of SSI of more than 50% (15.1% *vs.* 7%). All the studies considered in this review had in common the core elements of the SSI-reduction bundles, namely antibiotic prophylaxis, prevention of hypothermia, hair removal, prevention of hyperglycaemia[72]. Other interventions have been suggested, such as no fluid overload, skin preparation with chlorhexidine, double gloving or change of gloves and gowns before closing the fascia, lavage of subcutaneous tissue and silver dressing[23].

POSTOPERATIVE STAGE

Postoperative analgesia

Control of postoperative pain has always been a hot topic, as it is one of the variables that may affect postoperative recovery. The traditional use of morphine has always been quite effective, but at the expense of important side effects, such as prolonged ileus, and potential complications (respiratory, neurologic) and safety issues (drowsiness, dizziness, falls) in high risk patients. Several different analgesia regimens have been proposed, with the aim of minimizing patient discomfort while facilitating his or her recovery and minimizing side effects and complications of drugs. We agree with the American Society for Enhanced Recovery (ASER) that a completely painless surgery is a non-achievable goal[73], so we should aim at the best possible analgesia that does not impair the patient's physical recovery. Every analgesic regimen must also take into consideration the kind of surgical approach, as the requirements of pain control may vary according to the size and shape of the abdominal incision and the subsequent surgical trauma.

Opioids have been extensively used in the past to control postoperative pain, but at the expense of heavy side effects such as constipation, ileus, nausea, urinary retention, over sedation, delirium and delayed discharge. Clearly, this does not fit with the ERAS principles. The further demonstration, that non-opioid analgesia may be associated with less pain, reduced risk of cancer recurrence and longer survival[74] has convinced the medical community that non-opioids regimens should be considered. The European guidelines suggest using opioids only as rescue analgesia, in particular in laparoscopic surgery. The ASER guidelines suggest a multimodal approach with NSAIDs, paracetamol and/or gabapentin, eventually associated with spinal/epidural analgesia and/or local anaesthetic infusion within the wound. Eventual adjuncts can be steroids, ketamine and tramadol[73].

It has been demonstrated that the neuro-axial block is able to reduce the surgical stress by interrupting the transmission of the nociceptive stimulus to the brainstem, thus reducing the risk of postoperative ileus[2,75]. Epidural analgesia is also effective for the pain control in the postoperative period, even if many Authors prefer to limit its use to laparotomic surgery where its benefits are definitely clearer than the risks. Epidural anaesthesia (EA) is associated with very good pain control after colorectal surgery, both laparoscopic and open, but the prolonged block of the sympathetic system, with consequent hypotension and need for continuous fluid infusion, is a major concern. Although the benefits of EA are well known[76], the use of single-injection intrathecal (spinal) analgesia (IA) with opioid plus or minus local anaesthesia is gaining favor[77]. The main advantage of IA with respect to epidural is its easiness, as it does not require any further equipment or specific surveillance. The perceived drawback is its potential risk of complications such as respiratory depression. This has been widely contradicted by scientific evidences[77]. On the contrary, IA is safe and effective, as it is able to control postoperative pain while allowing earlier functional recovery and shorter LOS[78]. IA is usually performed to provide additional pain control in association with paracetamol and NSAIDs.

Peripheral analgesia can also be extremely effective. Transversus abdominis plane infiltration, wound and peritoneal infiltration and rectus sheath block in association with systemic analgesia have all been demonstrated to be able to reduce the use of opioid with respect to systemic analgesia only[73].

All non-opioid oral analgesic agents have been widely used and have been found to be able to reduce the use of opioids. Their routine use is part of any ERAS programme. Intravenous administration of paracetamol can achieve higher plasma concentrations with respect to the oral administration, but there is no evidence of a clear superiority of intravenous versus oral administration in the clinical settings[79]. The use of NSAIDs has been recommended on the basis of good efficacy and insufficient evidence of complications[80]. However, recent evidence suggest caution with the use of non-selective NSAIDs like diclofenac, due to increased risk of anatomotic leak[81]. Gabapentin and pregabalin can also be used to reduce the requirement of opioids in the postoperative period[82], and as such their use is recommended by the ASER[73], but only at high doses. Tramadol[83], ketamine[84], magnesium[85] and steroids[86] have all been used for postoperative pain control, with some efficacy, but their use has not gained wide acceptance.

Prevention of postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) are common side effects of surgery and anaesthesia and can affect early feeding and reduce patient satisfaction. Recent guidelines suggest a multimodal and quite liberal approach to PONV treatment[23]. Avoidance of opiates and administration of oxygen can help reducing PONV. Goll *et al.*[87] demonstrated that 2 h of 80% oxygen are more effective in reducing PONV than ondansetron. However, postoperative ondansetron following preoperative administration of dexamethasone is an effective combination[23]. It is well known that intravenous anaesthesia with propofol is superior to inhalation anaesthesia[88], but the role of gabapentin is not yet fully defined[23].

Prevention of postoperative ileus

Postoperative ileus still remains a major problem after colorectal surgery, and in particular after extensive rectal operations, with a prevalence rate as high as 28%[89]. Its global impact on LOS overlaps the impact of anastomotic leak[90]. Its etiology is multifactorial and usually is not related to a substandard surgical technique. Smoking, major laparotomy, ASA classification and duration of surgery were considered independent causative factors[91,92]. Molecular level evidence has recently demonstrated the role of intestinal microbioma in the regulation of bowel motility[93], possibly through its action on bowel macrophages, whose activation leads to generalized intestinal nervous plexa dysfunction and paralytic ileus[94]. This can be taken as a confirmation of the positive role of oral non-absorbable antibiotics in the preparation of the bowel for colorectal surgery[49], even if the exact mechanism of action and the bacteria species involved in the process are not yet fully understood[50].

Compliance with ERAS principles is a protective factor against postoperative ileus[95]. According to ERAS principles, early recovery of bowel peristalsis is based on four cornerstones: (1) mini-invasive technique; (2) restrictive fluid infusion; (3) avoidance of opiates; and (4) early re-feeding.

Multiple RCTs and meta-analyses have demonstrated that early feeding stimulates recovery of bowel function[23,96]; this is particularly true in younger patients operated on by subspecialist colorectal surgeons using laparoscopic techniques[97,98].

It is well known that opioids may impair the gastrointestinal motility through a direct action on the mu-receptors of the bowel, causing ileus and constipation. Therefore, the use of peripheral opioid antagonists may reduce the risk of postoperative ileus[97]. Although this has been incorporated into the American ERAS guidelines[23], some Authors suggest prudence as definitive evidence is not yet available[98]. A recent phase 2 study from Scotland confirmed that oxycodone and naloxone reduces time to first bowel motion when compared to oxycodone only within an ERAS protocol in laparoscopic colorectal surgery, but the authors admit that a proper RCT is still needed[99].

It has been proposed that chewing gum may stimulate bowel motility - via vagal stimulation or gastro-intestinal hormones secretion - with an earlier return of intestinal function and reduced LOS[100], but unfortunately the vast majority of colorectal studies are small sized and of poor quality[101,102]. A large RCT on 402 patients clearly demonstrated that, although there is no detriment, there is no beneficial effect either[103]. Although chewing gum has been added to the ERAS Society guidelines[18], this matter remains unclear.

The use of oral laxatives such as magnesium oxide and disodium phosphate can reduce the time to first bowel motion[104], but it has not been fully evaluated yet and it is considered a weak recommendation[18].

Postoperative nutrition

Early studies confirmed that early oral feeding after a colorectal operation does not increase the risk of complications and, on the contrary, can be beneficial in reducing the post-surgical catabolism, improving the immune function, reducing the systemic inflammatory response and reducing bacterial translocation. The ERAS protocols suggest early re-feeding with liberal fluid intake by mouth immediately after surgery, provided that PONV is well controlled, and early return to a normal diet[18]. In cases where oral feeding is not deemed to be sufficient to get a correct caloric intake, it may be necessary to add oral proteic supplements[18].

Even if the application of simple rules can yield great results, the implementation of a specific gastrointestinal rehabilitation programme resulted in further reduced morbidity and LOS[105].

Immunonutrition is associated with reduced rate of complications and reduced length of stay[106,107]. In fact, it has been demonstrated that the administration of nutritional supplements containing mainly glutamine, arginine, omega-3 fatty acid and ribonucleic acid is able to reduce the inflammation and improve the immune response. The mechanism of action of immunonutrition has not been fully clarified yet. Apparently, its main effect is to reduce bacterial translocation by maintaining the integrity of the intestinal mucosa and reducing its permeability, thus reducing the risk of infectious complications[107].

The main barrier to a correct postoperative nutrition is patient information[108], so once again it is important to emphasize the need for patient engagement also in nutritional care at the preoperative encounters[109].

Early mobilization

Early postoperative mobilization has beneficial effects on the whole postoperative recovery. In fact, it reduces catabolism and bowel recovery and improves ventilator function and bronchial clearance (reducing the risk of pneumonia and atelectasis), reduces the risk of DVT and prevents muscle loss and insulin-resistance. Ultimately, it reduces postoperative LOS, encourages independence and reduces discomfort[18]. Several different modalities and targets have been proposed[23], but no specific protocol has been identified. A frequent approach is to allow liberal mobilization as soon as possible after surgery[23], but in high risk patients, strong support by specialized staff may be needed.

Quality control

Auditing outcome data is the only way to improve the service we are offering. Once an ERAS programme has been started, it is likely that this will become part of the "routine" management of surgical patients. Nonetheless, there is good recent evidence that habituation can lead to over-confidence and the application of some of the ERAS elements can reduce with time[110,111]. The exact quality indicators of ERAS protocols are yet to be defined, but it is obvious that LOS is not necessarily the main endpoint. Fit-for-discharge as a parameter can be more reliable than LOS[112]. The ERAS Society recommends also considering morbidity and mortality, need for transfusions, duration of surgery, readmission rate and total cost. We would also add reoperation rate and patient satisfaction as key factors for quality control. Moreover, it must be emphasized that the ultimate aim of rectal resection is to cure a malignant condition; therefore we believe that oncologic outcomes, such as rate of radical resections and rate of adequate lymphadenectomies must also be taken as quality parameters.

Another parameter that must be recorded and audited is the compliance with the elements of ERAS. Engagement of the whole multidisciplinary department is paramount and adherence to the process is crucial to obtain the advantages of ERAS[17,113].

To the best of our knowledge, adherence to ERAS protocols has never been analysed in relation to the size of the department, however we feel that in a small department it should be relatively easy to implement the necessary changes leading to the full potential of ERAS principles, with respect to a big-size department where engagement of all the relevant people can be tricky and sometimes frustratingly impossible. One of the Authors' past experience with implementing ERAS in a rural hospital has shown that evolutionary changes aiming at improving postoperative recovery in colorectal surgery can be implemented relatively quickly, and the learning curve of the whole team is quite short[5]. In more sizeable departments, the introduction of the ERAS protocol should be more gradual, focusing initially on prevention of hypothermia, early postoperative feeding, early removal of the bladder catheter and no nasogastric tube[114]. Actually, the Perioperative Italian Society who released this statement in a very recent publication added no bowel preparation to the "core" items listed above, but on this subject we favour the American guidelines, suggesting selective bowel preparation. Although a gradual approach can be acceptable, we again agree with the American guidelines that the aim must be a complete and standardised protocol implementation[23].

Probably never, have such minimal changes in surgical organisation and mindset yielded such a huge return as with ERAS in colorectal surgery[4].

CONCLUSION

ERAS protocols are largely improving the experience of patients undergoing colorectal surgery but they also represent a huge step forward in team working, hospital dynamics and trust finances, as they reduce LOS, total hospital costs and pharmacy costs, with a contemporary reduction of complications and readmission rates[115]. In a world where new scientific evidences are published on daily basis it is normal that ERAS principles are still quite fluid, but this is not necessarily a bad thing. Some of the ERAS elements are particularly likely to change in the near future, such as the attitude towards MBP and oral antibiotic, prehabilitation and immunonutrition. We can expect that with increased experience and awareness, LOS will reduce with time and more and more patients will be operated as day cases in the future.

Despite the various attempts at standardisation, ERAS statements remain general principles whose dynamic application must be adapted to the local situation and to the team preferences and must show an ample degree of flexibility. For this reason, every team applying ERAS standards must keep in mind the need for regular audits, quality checks and improvement.

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Author's contributions

Literature selection and review, article drafting, and approved the final version: Tebala GD, Gordon-Dixon A, Imtiaz M, Shrestha A, Toeima M

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Mini-invasive Surgery

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Laparoscopic hepatectomy for benign hepatic lesions: short and long-term outcomes including quality-of-life evaluation

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Abstract

Aim: Even though laparoscopic hepatectomy (LH) has proved to be both safe and effective in specialized centers; the restricted indications for resection in the case of benign liver lesions has resulted in poorly reported outcomes. Our aim was to describe the short and long-term results of LH to treat benign hepatic lesions, including quality of life (QoL) evaluation.

Methods: Thirty-one LHs were performed between 2007 and 2018 in 30 patients. We evaluated QoL with the SF-36 test and a body image satisfaction questionnaire by personal interview before surgical treatment and at 1 month, 3 months, 6 months and 1 year after surgery.

Results: Median age was 38 years (range 21-71) and the majority were females (68%). The most frequent etiology was hepatic adenoma in 16 patients (52%), followed by focal nodular hyperplasia (*n* = 4), cavernous hemangioma (*n* = 3), hepatic abscess (*n* = 3), cystadenoma (*n* = 5) and hepatolithiasis (*n* = 1). The majority of resections were minor (66%) and the conversion rate was 6.2%. Pathological examination confirmed negative margins in all patients. Postoperative mortality was nil, while morbidity was 6.2%. Median hospital stay was 4 days (range 1-32 days). In a median follow-up of 48 months (range 2-120), 2 patients experienced recurrence. QoL variables were similar between the preoperative and postoperative periods.

Conclusion: LH should be considered the main therapeutic approach for treating selected patients with benign liver lesions who require surgical resection because it presented both null mortality and low morbidity, along with rare recurrence, a good quality of life and high esthetic satisfaction.

Keywords: Laparoscopic liver surgery, liver neoplasms, adenoma, liver cell, focal nodular hyperplasia, hemangioma, cavernous, quality of life

INTRODUCTION

Since the early 90s, when the first laparoscopic anatomical resection of the liver was reported, laparoscopic hepatectomy (LH) has gained increasing importance for treating hepatic tumors[1]. Several advances in laparoscopic instruments such as parenchymal transection devices, staplers and hand-assisted equipment, together with improved expertise in laparoscopic surgery, have led to increasing use of LH, especially in referral centers. Given its many advantages over open hepatectomy, including less postoperative pain, less use of opiate analgesia, better cosmetic results, decreased blood loss, decreased postoperative complications (both hepatic-specific and pulmonary) and shorter hospital stay, LH has become the preferred approach for treating benign hepatic tumors[2-7]. Even though LH has been shown to be both safe and effective; the restricted indications for resection in the case of benign liver lesions have resulted in poorly reported long-term outcomes. In addition, there is a need to know whether LH might improve the overall postoperative quality of life (QoL) of patients with benign lesions[8-15].

The aim of the present study was to evaluate the short and long-term outcomes of LH for benign liver tumors, with special emphasis on postoperative QoL results.

METHODS

Between June 2007 and March 2018, 81 LHs were performed by a single surgical team in two hospitals (Hospital Santa Lucia between 2007 and 2014 followed by Hospital Brasilia between 2014 and 2018). Of these, 31 (38%) LHs performed in 30 patients bearing benign hepatic lesions formed the study population.

The indications for resection of benign liver lesions were as follows: symptomatic patients, presence of cystadenoma, presence of hepatolithiasis and uncertain diagnosis based either on imaging or on biopsy findings (when it was not possible to rule out malignant hepatic neoplasm). Hepatic adenoma (HA) was also resected in the following circumstances: larger than 4-5 cm, female gender with intention to conceive, presence of beta-catenin mutation or male gender. Resection of pyogenic liver abscess (PLA) was indicated after failure of percutaneous drainage. All patients were studied with serum tumor markers (CEA, AFP and Ca 19.9), abdominal ultrasonography, computed tomography and magnetic resonance imaging (MRI). For the last seven cases, MRI with hepatobiliary contrast (Primovist; Bayer-Schering, Berlin, Germany) was also carried out. Since 2007, our team has considered the laparoscopic approach as the first choice for all hepatectomies except in the following situations: very large lesions (> 10 cm) in the right lobe, tumors close to major vascular structures, or central locations. All liver resections were defined in accordance with the International Hepato-Pancreato-Biliary Association terminology through the Brisbane Nomenclature, 2000. Major hepatectomy was defined as resection of three or more hepatic segments. The surgical techniques used for LH were either the intra-hepatic Glissonian approach [Figures 1 and 2] or the extra-hepatic Glissonian approach [Figures 3 and 4], in accordance with previous standardization[7,11-13]. Intraoperative ultrasonography was performed whenever available. Surgical specimens were preferentially removed in an Endobag [Figure 5], by means of a Pfannenstiel incision [Figure 6] or a small right subcostal incision. On the liver bed, a hemostatic Surgicel was used, along with fibrin glue (Eviscel) when available, to finish the hemostasis. Finally, drains were placed only for major hepatectomies. Postoperative morbidity

Figure 1. Intrahepatic Glissonian approach for right posterior sectionectomy. Demarcation of liver surface around right posterior Glissonian pedicle

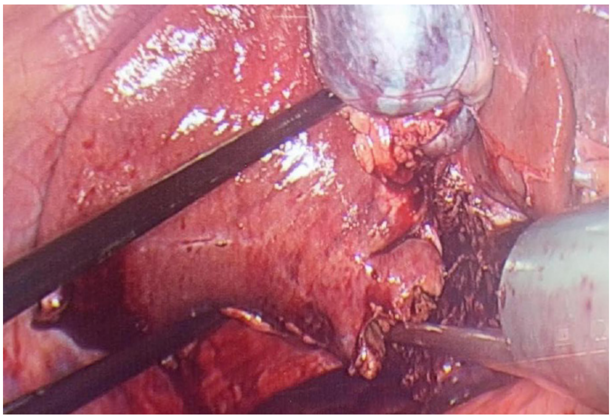

Figure 2. Intrahepatic Glissonian approach for right hepatectomy. En-bloc stapling of right glissonian pedicles by means of vascular stapler (after two hepatotomy procedures)

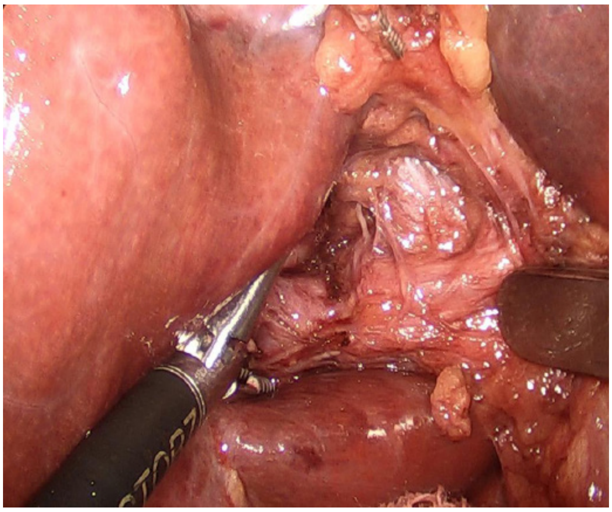

Figure 3. Extra-hepatic approach. En-bloc dissection of the right posterior hepatic pedicle

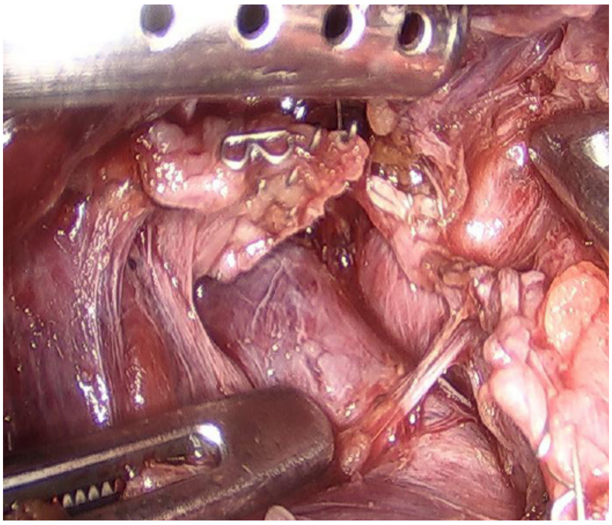

Figure 4. Extra-hepatic approach. Right posterior hepatic pedicle stapled en-bloc

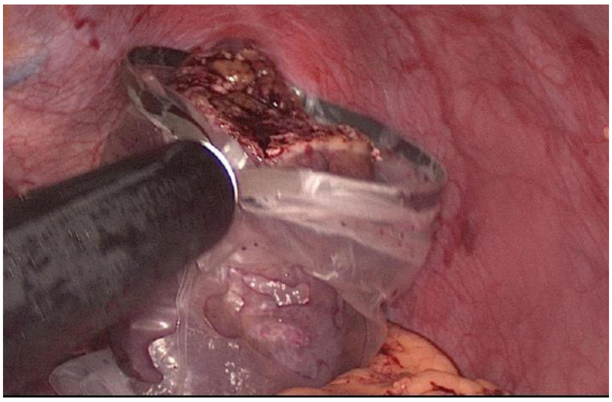

Figure 5. Segmentectomy 3 surgical specimen placed in Endobag before retrieval

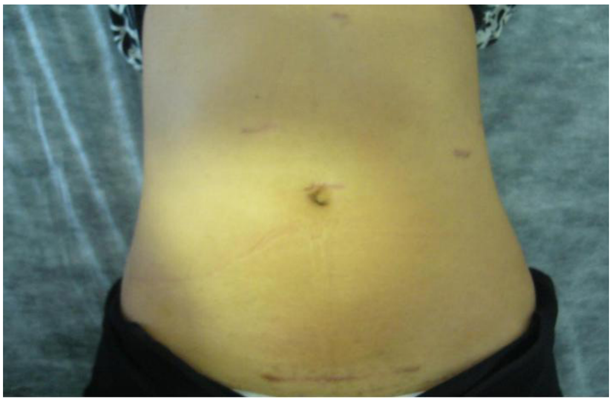

Figure 6. Late result after left lateral laparoscopic segmentectomy

Table 1. Patient Characteristics

Variable	Value
Gender, female, *n* (%)	21 (70)
Age, years, median (range)	38 (21-71)
ASA risk score, *n* (%)	
1	28 (93)
2	2 (7)
3	
Previous open abdominal surgery, *n* (%)	6 (20)
Etiology, *n* (%)	
Adenoma	16 (50)
Cystadenoma	5 (17)
Focal nodular hyperplasia	4 (13)
Pyogenic liver abscess	3 (10)
Hemangioma	3 (10)
Non-oriental hepatolithiasis	1 (3)
Number of lesions, median (range)	1 (1-6)
Lesions size, cm, median (range)	5 (3-13)

was defined in accordance with the Clavien-Dindo classification of surgical complications[16]. Biliary fistula was defined using the International Study Group of Liver Surgery classification[17]. Follow-up included physical examinations and hepatic blood tests every three months, as well as abdominal imaging (CT or MRI) twice a year. Recurrence was considered when a lesion reappeared on imaging examinations and was finally confirmed by means of histological analysis. QoL was measured by means of a QoL questionnaire using the Short-Form Health Survey (SF 36), as previously reported by Giuliani *et al.*[15]. This test was administered by means of a personal interview before surgery and at 1, 3, 6 and 12 months after surgery. In addition, a simple non-validated questionnaire was also performed including the following questions: (1) satisfaction of surgical scar; (2) exposure of body image when wearing bikinis, shorts, "summer clothes", *etc.*; (3) change of daily behavior (social, type of the clothes, sportive practices); and (4) recommendation of the LH to other patients. The responses were classified into positive or negative. All these questions were considered to evaluate body image satisfaction regarding the esthetics aspects after LH.

Statistical Analyses

Categorical variables are described using percentages. Continuous variables are expressed as means and standard deviation for symmetrically distributed, and median (range) for nonsymmetrically distributed data. Differences in SF-36 QoL questionnaire scores between preoperative evaluations and postoperative evaluations were analyzed using two-way repeated measures ANOVA and each patient was in his or her own control at the time of the evaluation. There were no significant outliers in pairwise comparisons and normality assumption held at Shapiro-Wilk test using residuals. We used Wilks' lambda as an omnibus test statistics for differences between the means of QoL evaluations. Within-subjects effects were evaluated by F-test with Greenhouse-Geisser correction due to unequal variances of the differences between all combinations of related groups, as assessed by Mauchly's test. Post hoc pairwise comparisons were calculated with Bonferroni adjustment for multiple comparisons. We reported exact P values up to 0.001 and the significance level was set to 0.05 (5%) for statistical inference. Statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Hong Kong, 2015).

RESULTS

The general characteristics of the study population are detailed in Table 1. Median age was 38 years (range 21-71) and the majority were females (70%). The most frequent etiology was HA in 16 patients (50%). Among symptomatic patients (n = 3) who underwent LH, two of them had giant hepatic hemangiomas while the third patient had a giant focal nodular hyperplasia (FNH). Their symptoms were as follows:

Table 2. Operative characteristics and postoperative outcomes

Variable	Value
Type of hepatectomy, *n* (%)	
Right hepatectomy	4 (12.9)
Left hepatectomy	6 (19.3)
RPS	8 (25.8)
LLS	8 (25.8)
Segmentectomy 5	2 (6.4)
Segmentectomy 6	1 (3.2)
Segmentectomy 3	1 (3.2)
Segmentectomy 2	1 (3.2)
Operative time, min, median (range)	135 (60-265)
Blood loss, mL, median (range)	125 (0-1000)
Major morbidity, *n* (%)	2 (6.2)
Mortality, *n* (%)	0 (0)
Hospital stay, days, median (range)	4 (1-32)
Time to normal activities, days, median (range)	14 (7-32)

RPS: right posterior sectionectomy; LLS: left lateral sectionectomy

abdominal pain and sensation of epigastric fullness (n = 2) and visceral compression (n = 1). For most patients, preoperative diagnosis was made from typical findings seen on either CT or MRI. Three patients with HA underwent a percutaneous biopsy that confirmed the presence of beta-catenin mutation. One patient underwent intraoperative frozen-section biopsy because preoperative examinations presented a differential diagnosis with hepatocellular carcinoma, and FNH was then confirmed in this case. There were 3 patients who presented multiple lesions, 1 patient had 6 lesions (FNH) and 2 patients had 3 lesions each (HA).

Thirty-one liver resections were performed in 30 patients (1 patient underwent 2 independent resections, both of them by means of a laparoscopic approach). The majority of liver resections were minor (64.5%) and there were two open conversions in this series (6.4%). One patient underwent conversion due to severe intraoperative bleeding (> 750 mL) and the other due to technical difficulties. The first was an obese male operated on for a 10 cm symptomatic giant hemangioma in the dome of the left liver, very close to the left hepatic vein, which was injured due to a stapler failure. The stapler was fired but it was not possible to open it and, thus, an open repair became necessary. This patient was the only one in this series who required postoperative blood transfusions (3.3%). The second case was a female with a cystadenoma in the left lobe who presented multiple adhesions between the small intestine and the liver due to a previous surgery. Pringle maneuver was performed in a single case who underwent open conversion due to intraoperative bleeding. Eight patients underwent surgical drainage of the liver bed by means of a tubular drain. Details of the surgical procedures are shown in Table 2.

Two patients (6.4 %) presented postoperative complications (grade 3), and these were the same 2 patients who underwent open conversion [Table 2]. One patient presented a biliary fistula that required endoscopic retrograde cholangiopancreatography with stent placement, and the other developed an incisional hernia that required a laparoscopic repair six months after surgery. There was no gas embolism in this series. Mortality was nil. The median hospital stay was 4 days (range 1-32 days) for the overall series, and 2 days (range 1-3 days) considering only the minor resections. Eighteen patients required low doses of common analgesics for 2 or 3 days during their postoperative course, while 10 patients required them for 4 days and 2 patients for 6 days. Both patients who underwent open conversion required narcotic analgesia. The median length of time taken to return to normal daily activities was 14 days (range 7-32 days) for the overall series, and 9 days (range 7-12 days) considering only the cases of monosegmentectomy. These findings are shown in Table 2. Among the symptomatic patients, all of them achieved complete symptom relief. Histological examination confirmed negative surgical margins in all patients. Preoperative diagnosis was confirmed in all but 2 patients (93%), who underwent oncological LH because of typical features of hepatocellular carcinoma on preoperative imaging (wash-in/wash-out), but definitive pathological evaluation showed HA in both cases. The median length of follow-up in this series was 48 months (range 2-120 months). Two patients experienced disease recurrence during follow-up. The first recurrence occurred in a young woman two years after right posterior sectionectomy due to HA. She developed a new HA in the left lobe and finally underwent a successful laparoscopic resection of segment III. The second recurrence occurred ten years after left hepatectomy for PLA in a 78-year-old man. He presented a new very large solid-cystic abscess in the right hepatic lobe (segments 7 and 8), for which he underwent open unroofing and finally died due to postoperative infectious complications and sepsis.

We observed a statistically significant decrease of the overall QoL in seven measured variables (except social) at early postoperative period until one month [Table 3]. However, after one month of the postoperative period we observed a statistically significant increase of the all Qol variables. Thus all Qol variables were similar between the preoperative and postoperative periods after 3 months from surgical intervention. These variables were maintained similar until 12 months. Both role emotional and mental health variables presented a great improvement after postoperative period [Table 3]. Application of the questionnaire to evaluate esthetic body image after surgery showed that 93% of the patients considered that their result was satisfactory. Only the two patients who underwent open conversion were dissatisfied with their esthetic result.

DISCUSSION

Since initial experiences, LH has been proven to be a good choice for treating benign hepatic lesions, especially for minor resections of lesions arising in easily accessible hepatic segments at anterolateral positions, so-called "laparoscopic hepatic segments"[2-6]. Since 2008, two major international expert consensus conferences have been held to review the role of LH. The first of these was held in Louisville, USA, where it was established that LH was best indicated for solitary lesions measuring 5 cm or less that were located in segments 2 to 6[6]. At this meeting, it was accepted that laparoscopy should be considered the standard approach for left lateral sectionectomy and that indications for surgical treatment of benign hepatic lesions should not be widened simply because laparoscopic approach was feasible. Six years later, a new consensus meeting involving many worldwide experts was held in Morioka, Japan, where hepatic resections of greater complexity became more accepted, including major resections or resections of posterosuperior liver segments, especially at referral centers[7]. Therefore, LH is nowadays considered a safe and feasible alternative to open operations, even for left or right major hepatectomies and malignant liver lesions.

Given that LH is a complex laparoscopic procedure, laparoscopic left lateral sectionectomy has been considered by many experts the ideal anatomical resection for initial training because of its anatomical accessibility and the possibility of using the aid of staplers[18-22]. Therefore, laparoscopic left lateral sectionectomy has been one of the most performed types of LH along the learning curve of many authors[8,10,12]. Even though laparoscopic left lateral sectionectomy and right posterior sectionectomy were the most frequent LHs performed in the present series, more complex LHs including left hepatectomy, right hepatectomy and even mesohepatectomy were also performed, reflecting the strong trend in the literature towards performing more complex procedures for treating hepatic lesions[2-13,15,23].

Many studies, including meta-analyses, have confirmed the benefits of LH in comparison with open hepatectomy, namely: lower levels of postoperative pain, fewer peritoneal adhesions, shorter hospital stay, earlier return to daily activities, lower blood loss, reduced morbidity, fewer operative complications and less mortality[2-15,18-29]. Among the short-term outcomes from our study, a low blood loss (mean 125 mL),

Table 3. QoL variables

Dimension	Time	Mean (SD)	Multivariate model[a]	Within subjects[b]	Baseline contrast[c]	Last period contrast[c]
Physical functionating	Baseline	96.9 (2.5)	< 0.001	< 0.001		
	1 mo	93.1 (5.5)			0.002	0.002
	3 mo	94.7 (5.2)			0.22	0.001
	6 mo	95.5 (4.9)			0.98	0.004
	12 mo	96.4 (3.9)			1.00	0.39
Social functionating	Baseline	99.4 (0.7)	0.48			
	1 mo	98.8 (2.9)				
	3 mo	99.3 (1.3)				
	6 mo	99.6 (0.7)				
	12 mo	99.7 (0.6)				
Mental health	Baseline	91.7 (5.1)	< 0.001	< 0.001		
	1 mo	93.2 (8.1)			1.00	1.00
	3 mo	95.8 (4.2)			0.002	0.29
	6 mo	97.9 (2.5)			< 0.001	0.023
	12 mo	97.2 (3)			< 0.001	1.00
Bodily pain	Baseline	97.4 (2.2)	< 0.001	0.032		
	1 mo	95.4 (6.2)			0.81	0.81
	3 mo	96.5 (4.5)			1.00	0.40
	6 mo	97.6 (2.8)			1.00	0.09
	12 mo	97.6 (2.8)			1.00	1.00
Vitality	Baseline	97.6 (4.5)	0.009	0.001		
	1 mo	96.4 (4.8)			0.29	0.29
	3 mo	95.7 (5)			0.044	1.00
	6 mo	97.2 (3.4)			1.00	0.007
	12 mo	98.5 (2.1)			1.00	0.035
Role physical	Baseline	93.1 (2.9)	0.008	< 0.001		
	1 mo	90.3 (5.6)			0.01	0.01
	3 mo	92.4 (3.8)			1.00	0.003
	6 mo	92.8 (3.4)			1.00	1.00
	12 mo	93.8 (2.9)			1.00	0.13
Role emotional	Baseline	89.5 (7.1)	< 0.001	< 0.001		
	1 mo	93.2 (5.2)			0.45	0.45
	3 mo	95.9 (3.6)			0.005	0.69
	6 mo	96.4 (3.1)			0.001	0.99
	12 mo	97.3 (2.7)			< 0.001	0.08
General health	Baseline	95.6 (7.6)	< 0.001	0.037		
	1 mo	97.5 (1.2)			1.00	1.00
	3 mo	98.7 (1.2)			0.26	< 0.001
	6 mo	99.1 (0.8)			0.11	0.61
	12 mo	99.4 (0.9)			0.24	0.83

[a]Wilks' lambda; [b]F-test with Greenhouse-Geisser correction for violation of sphericity; [c]post hoc pairwise comparisons with Bonferroni adjustment for multiple comparisons. SD: standard deviation

short hospital stay, low morbidity (6.4%) and no mortality are clearly in accordance with the many advantages reported in previous studies. The surgical margin was adequate in all cases, despite the lack of intraoperative palpation that is inherent to this method. Late recurrence in this series was a rare event (only 6%), and given that they occurred distant in liver parenchyma, they could perhaps be attributed to more aggressive biological behavior in those two cases.

Benign lesions of the liver usually occur in young patients, who care not only to achieve an early return to work and sports practice, but also to maintain a good QoL and a pleasing body image. Giuliani *et al.*[15] have demonstrated that the laparoscopic approach was superior regarding the QoL of patients who underwent operations due to benign liver lesions. In the present study we observed that there was an excellent

QoL among the patients who underwent successful LH without open conversion. Seven out of eight variables measured by the SF 36 questionnaire presented similar results between preoperative period and postoperative period (after three months of surgical procedure). In our view point, this finding may indicate that LH allows QoL maintenance in patients operated from benign diseases. In the present study, an early return to work and sports practice was observed and, since most of the patients were young and in a productive phase of their lives, a significant socioeconomic gain could be expected from this population group. The main limitations of this study are its retrospective nature, as well as the heterogeneous and relatively small patient population. However, to our knowledge, no case series in Brazil have evaluated early and late postoperative outcomes along with the QoL of patients after LH performed solely on benign lesions of the liver. In addition, this report is unique because most of the patients in this sample were young women who live in a tropical country where body image is a very important tool for evaluating the overall QoL. Thus, a simple satisfaction questionnaire was applied in addition to the QoL questionnaire and showed that about 93% of our patients were satisfied in relation to the general esthetic aspects of the laparoscopic approach.

In conclusion, LH presented low morbidity, null mortality and rare recurrence in the present series. Furthermore, LH offered a good QoL and high esthetic satisfaction. Therefore, LH performed by expert liver surgeons should be considered the main therapeutic approach for treating selected patients with benign liver lesions who require surgical resection. Further prospective studies are needed to confirm our findings.

DECLARATIONS

Author's contributions

Contribution to conception and design, and analysis and interpretation of data, giving the final approval of the version to be submitted and any revised version: Pais-Costa SR

Contribution to selection of the studies and literature which were included in the references and drafting the article and revising it critically for important intellectual content: Lima OAT

Contribution with acquisition and collection of data: Costa GC

Contribution to statistical analyses : Martins SJ

Availability of data and materials

Data of the patients were collected from their archives in Dr. Pais-Costa's personal clinic, Oncodigestiva - Digestive Surgery Institute. The patients only authorized this study.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there were no conflicts of interest.

Ethical approval and consent to participate

This study was approved by hospital ethics committee of Hospital Brasília. Consent to participate was obtained.

Consent for publication

Not applicable.

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Mini-invasive Surgery

Review

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Minimally invasive contact X-ray brachytherapy as an alternative option in patients with rectal cancer not suitable for bespoke surgical resection

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Abstract
Surgery remains the gold standard treatment for rectal cancer. All published guidelines and most protocols recommend surgery as the standard of care. However, non-surgical management of rectal cancer is increasingly gaining acceptance as it avoids extirpative surgery and a stoma. In patients who are not suitable for surgery because of advancing age or medical comorbidities, and also in a small number of patients who are stoma phobic and refuse surgery, we need to consider an alternative treatment option to bespoke surgery. External beam radiotherapy is usually offered as an alternative. However, local regrowth rate is high and contact X-ray brachytherapy (Papillon treatment) boost can be added to reduce the risk of local regrowth after external beam radiotherapy. Case selection is important to achieve the best results.

Keywords: Contact X-ray brachytherapy, watch and wait, papillon, rectal cancer patients not suitable for surgery

INTRODUCTION

Surgery remains the gold standard treatment for rectal cancer: all published guidelines and most protocols recommend surgery as the standard of care[1,2]. Selection of the best option for care is based on recommendations made during multidisciplinary team (MDT) meetings, which are now mandated in most countries to discuss treatment for all patients with rectal cancer. The majority of MDTs still recommend surgery even for early rectal cancer as this is regarded as the standard of care. However, non-surgical management of rectal cancer is increasingly gaining acceptance as it avoids extirpative surgery and a stoma[3]. In patients who are not suitable for surgery because of advancing age or medical comorbidities, and also in a small number of patients who are stoma phobic and refuse surgery, we need to consider an alternative treatment option to surgery[4]. In most cases, external beam radiotherapy alone (EBRT) or with chemotherapy (EBCRT) is offered as an alternative to surgery. It is likely that with EBCRT alone, 10%-30% of patients can achieve clinical complete response (cCR)[5,6]. For these patients, a "watch and wait" strategy can be offered that avoids extirpative surgery with a stoma. The published evidence indicates that in 25%-38% of cases, local regrowth can develop late after achieving a cCR following EBCRT alone[3,5]. In patients who are fit and agree to proceed, these recurrences require salvage surgery. Once the patient develops a regrowth, if they are not fit for surgery or if the patient refuse surgery, palliative care is the only available option and the majority will die from symptomatic progressive local regrowth. The burden of care for these patients can put strain on their health care providers as these patients can survive for months or even years. The alternative approach is to offer them contact X-ray brachytherapy (CXB, Papillon treatment) which can reduce the risk of local regrowth[4]. Case selection is important to achieve the best results.

Case selection for treatment

In patients who are not suitable for surgery, or in younger, medically fit patients who vehemently refuse surgery because of stoma phobia, an alternative treatment option is radical radiotherapy. There are two types of radiation: either external beam radiotherapy (EBCRT/EBRT) or CXB (using a Papillon).

The choice of radiation type and which treatment modality to start depends on: (1) stage of the tumor (cT1); (2) possible lymph node spread (cT2, cT3); and (3) size of the tumor (< 3 cm or > 3 cm).

Inclusion criteria for CXB alone for early rectal tumors with curative intent
(1) mobile exophytic early rectal cancer (cT1);
(2) well to moderately differentiated adenocarcinoma;
(3) tumor size < 3 cm;
(4) no evidence of suspicious lymph nodes;
(5) no evidence of distant metastases;
(6) tumor within 12 cm of the anal verge;
(7) patient suitable for long-term follow-up.

Exclusion criteria

(1) poorly differentiated adenocarcinoma;
(2) presence of lymphatic or vascular invasion;
(3) bulky rectal cancer involving more than half the circumference (> 3 cm);
(4) fixed rectal adenocarcinoma with deep ulceration (cT3, cT4).

TREATMENT STRATEGIES

Early small rectal cancers (cT1, cN0, < 3 cm)

When an asymptomatic early (cT1) small (< 3 cm) rectal cancer is diagnosed (which usually occurs through the national bowel cancer screening program), the standard of care is to offer the patient surgery that may involve abdominoperineal resection of the rectum (APER) if the tumor is low in the rectum (< 6 cm from the anal verge). If the patient is not suitable for surgery or refuses surgery, an alternative option is to offer them CXB (Papillon) alone[4].

More advanced larger rectal cancers (cT2, cT3a/cNo/cN1, > 3 cm)

If the tumor size is > 3 cm or if the tumor is at stage cT2 or cT3a, then the risk of lymph node metastases can be as high as 20%-30%. CXB alone is not suitable as the low energy X-rays have limited penetration that will not reach the lymph nodes in the meso-rectum. The usual standard of care is to offer these patients surgery[1,2]. However, if the patient is not suitable for surgery or refuses it, they can be offered an alternative treatment using external beam radiotherapy with or without chemotherapy. If the patient is fit, external beam chemo-radiotherapy, with a total dose of 45 Gy in 25 fractions over 5 weeks, or a biologically equivalent dose, can down-size the tumor. There is published evidence that in radio-responsive tumors[6], the malignant tissue is not just down-sized, but usually down-staged to either ypT0 or ypT1 as well. If the patient is not fit enough for this treatment or has a poor renal function, a short course of radiation (25 Gy in 5 fractions over 5 days) can be offered, with consideration of performing CXB boost after 4-6 weeks to improve local control[4,7].

TECHNIQUES

CXB uses a high dose (90 Gy) of low energy (50 KVp) X-rays which are targeted directly on the tumor under visual guidance. There are two machines currently available for CXB cancer therapy. First, the Papillon + X-ray brachytherapy unit is currently marketed by the British company Ariane Medical Systems, Ltd (Alfreton, UK). Additionally, the Xoft® Axxent® Electronic Brachytherapy System® (iCAD, Inc., San Jose, CA, USA) is currently only approved for breast, skin and gynecological cancers, but it is undergoing development for treatment of rectal neoplasms. The radiation dose applied at each treatment is quite high (30 Gy) but because the radiation energy is low (50 kV) and applied directly to the tumor in a small volume (< 5 cc), the collateral damage to the normal surrounding tissues is limited. The treatment is given three times (30 Gy X 3) every two weeks. This regimen allows the normal tissues to recover during the 2-week break. There are three applicator sizes available: 30, 25 and 20 mm. The choice of applicator size depends on the tumor size which should be less than 30 mm (if the tumor size is > 30 mm, then EBCRT or EBRT is offered initially to down-size the tumor before CXB). The tumor is treated with a margin of 5 mm. In a responsive tumor, the lesion usually regresses centripetally [Figure 1], beginning immediately after the first fraction but mostly after the second fraction as illustrated in our case study[4,7].

The treatment can be given as a day patient as the whole procedure usually takes less than 30 min. This includes the initial assessment with endoscopy and the treatment time is less than 150 s. The patient can be treated supine or prone, in a knee-chest position [Figure 2]. A rigid sigmoidoscope is inserted to assess the tumor size, position, and to select the size of the rectal applicator. Then the radiation is applied using a suitable rectal treatment applicator. The radiation dose of 30 Gy is delivered to the surface of the normal surrounding rectal mucosa. Therefore, exophytic lesions which protrude into the treatment applicator receive a much higher dose of radiation than 30 Gy at the surface of the tumor. In a radio-responsive tumor, the treated layer is shaved off after each radiation treatment until the tumor regresses completely to the base of the bowel wall, and finally is flush with the surface of the surrounding normal rectal mucosa. The deeper layers then get treated with subsequent fractions. At a depth of 5 mm below the surface of the rectal mucosa, where the muscularis propria (deep muscle) of the rectal wall is situated, the dose of CXB is reduced to 50% of the surface (applied) dose, and at a 10 mm depth, the dose is attenuated to 30% of the surface dose [Figure 3]. There is published evidence that 98% of the residual tumor is usually confined within the muscularis propria (5 mm deep from the rectal mucosa) for early stages (cT1, cT2) of rectal tumors[6]. We normally offer CXB boost treatments 4-6 weeks following EBCRT. However, if the residual tumor following EBCRT is still bulky and infiltrates more than 5 mm below the rectal mucosa (beyond the rectal wall full thickness) we can delay the treatment by few more weeks to see if there is further regression of the residual tumor before proceeding with the CXB boost.

Follow-up

The risk of local neoplastic regrowth is usually highest within the first 2 years[4,7] and close follow-up is

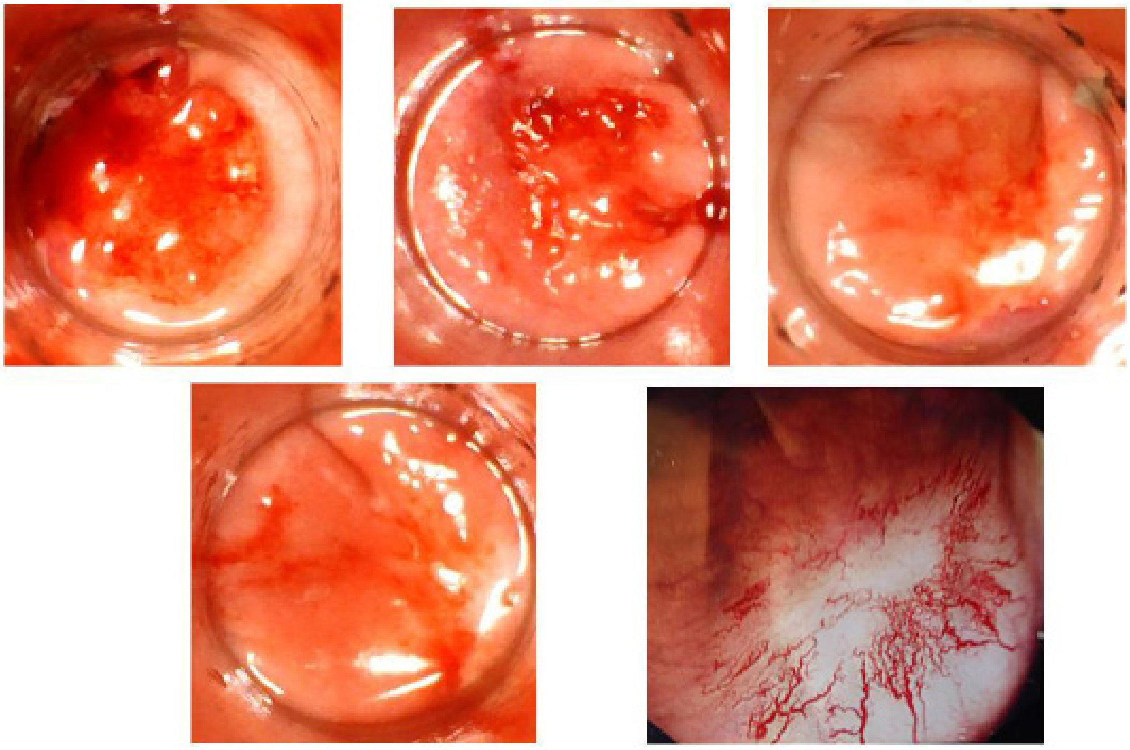

Figure 1. Treatment response to contact X-ray brachytherapy (CXB). Case 1: 65-year-old male diagnosed with low rectal adenocarcinoma staged as cT1cN0cM0 on MRI and CT scan. Refused surgery including trans-anal endoscopic microscopic surgery (TEMS) and external beam radiotherapy. Patient's choice. Treated only with CXB. Started his treatment in December 2012 after informed consent. Fully understand and accepted that CXB is non standard treatment for rectal cancer. Significant regression of tumour after only one fraction of CXB and no palpable or visible tumour after 2nd fraction. Clinical complete response (cCR) maintained after 5 years with good quality of life and bowel control. No bleeding despite being on clopidrogel

important during this period. Most of the regrowth is intraluminal[8] and can be detected by endoscopic examination, which should be carried out every 3 months during the first year, every 3-4 months during the second year, and every 6 months from the third to the fifth post-treatment year. Full colonoscopy should be done at 5 years if not performed earlier. Usually a digital rectal examination (DRE) is carried out just before inserting the endoscope for this procedure to assess any palpable local regrowth and its mobility. High-resolution whole-pelvis magnetic resonance imaging (MRI) should be done every 3-4 months during the first 2 years and at 6-month intervals in the third year to detect local and/or nodal regrowth. Computerized tomography (CT) scan of the chest, abdomen and pelvis should be done every 6 months during the first 3 years to detect distant metastases. The risk of both local and distant metastases is low after 3 years. Therefore, we do not recommended routine radiological examinations unless there is suspicion of a persistent tumor or development of distant metastases[7]. We advocate regular follow-up of the patients in the center where the treatment was delivered initially, by the same observer (if possible) or by a dedicated clinician following a "watch and wait" program. Patient follow-up also can be performed at the referring center, alternating with the CXB treatment center, by a limited number of clinicians who are experienced in the watchful waiting protocol. The radiological examinations should be done under a strict rectal protocol and reported by a radiologist familiar with the "watch and wait" clinical strategy,

Figure 2. Treatment set up position

because interpretation of the images can sometimes be challenging. If necessary, these images should be referred to an experienced radiologist for review. Likewise, endoscopic examination should only be done by experienced clinicians familiar with the "watch and wait" follow-up process for these cancers. It is important not to biopsy normal mucosa or non-cancerous radiation-induced ulcers as the negative predictive value of a benign rectal biopsy is of very limited value. Moreover, complications such as perforations, delays in wound healing, protracted bleeding, or persistent pain can occur if the tumor is very low in the rectum[9]. In addition, fibrosis following a biopsy can make the interpretation of the subsequent radiological images more difficult. If there is uncertainty regarding abnormalities, either on endoscopy or in the interpretation of radiological images, the best approach is to refer the patient back to an appropriate cancer center for further assessment. In uncertain cases, it is best to repeat the investigations sooner (within 6-8 weeks) to assess any changes and refer the patient back to the cancer center for an expert opinion. If there is local regrowth of the tumor, the appearance will change at that site, but the changes usually are subtle and progress slowly. Examination under anesthesia for a targeted deep biopsy may be necessary to identify local regrowth, but this is not mandatory, as most regrowth are embedded deep within the muscles (muscularis propria) and it is not always possible to get the histological evidence of local regrowth unless the whole area is removed surgically.

CXB for local persistence of tumors after EBCRT

The watch and wait protocol with deferred surgery can be offered to patients who achieve cCR following EBCRT or EBRT. However, the majority of patients (74%) have residual tumor reported following EBCRT or EBRT[6] and the standard of care is to offer these patients surgery. However, if the patient is a not suitable surgical candidate or still refuses surgery, CXB can be offered as a booster therapy. There is published evidence that some of these patients can achieve cCR following CXB boost for their residual tumor[4,7]. Patients can then be follow up by the 'watch and wait' strategy and avoid immediate surgery.

Residual tumors after CXB and EBCRT

If there is residual tumor following EBRT and CXB boost, surgery can then be offered. For small residual

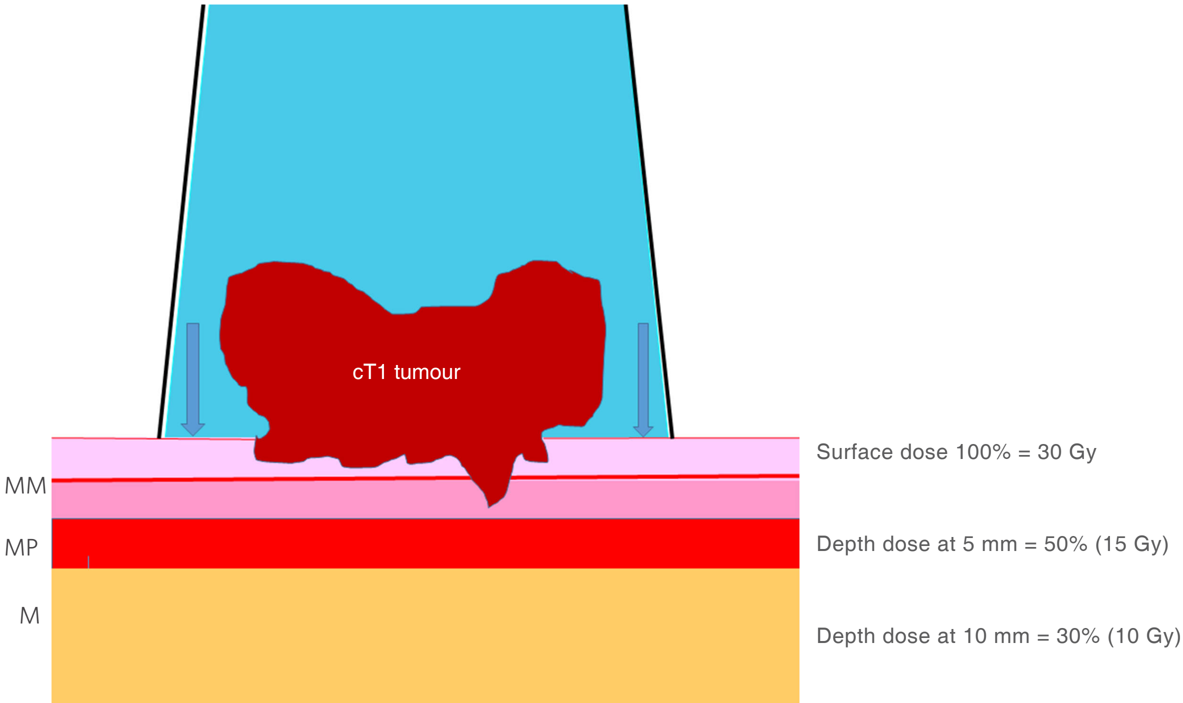

Figure 3. Treatment diagram and depth dose. MM: muscularis mucosa; MP: muscularis propria; M: mesorectum

tumors, trans-anal endoscopic microscopic surgery (TEMS) can be offered, because a proportion of residual mucosal abnormalities turn out to be benign adenomas that are difficult to differentiate from residual adenocarcinomas[10]. For gross residual tumors, salvage total mesorectal excision (TME) surgery should be offered[11]. However, the patient may not be medically fit for TME surgery or may refuse it. However, in our experience, at this stage most patients will agree for surgery, as they have tried the alternative non-surgical route and accept that this has failed. It is important to stress to the patient during the informed consent process that not all rectal cancers respond to CXB boosts after their EBRT, and that they may need to undergo salvage surgery if there is persistent residual tumor or a local growth at a later date[4,7].

Surgical salvage for local regrowth after cCR following EBCRT or EBRT and CXB

Local regrowth of a rectal cancer after achieving cCR following EBCRT or EBRT and CXB boost can be successfully treated if the patient is fit and agrees to surgery. Unfortunately, not all patients with local regrowth are fit and willing to undergo surgery[8]. Local regrowth following EBCRT or EBRT and CXB reportedly occurs in 11%-12% of cases[4,6,12,13], a rate that is much lower than the 25%-38% local regrowth that has been reported following EBCRT or EBRT alone[3,5].

DISCUSSION

Most colorectal cancer treatment protocols and guidelines do not include radiotherapy for early rectal neoplasms[1,2]. Most colorectal MDT recommendations do not advocate non- surgical treatment even for early rectal cancers detected by screening. The dilemmas arise when a patient refuse the MDT recommendations. The UK National Institute for Health and Clinical Excellence (NICE) guidelines state that patients can refuse medical interventions to the extent of electing to undergo no treatment[14]. Most clinicians will only consider alternative treatment options if there is no evidence from a randomized trial. It is not always possible to do a randomized trial when two treatment strategies are not in equipoise with entirely different outcomes. In the absence of data from "hard to do" randomized trials, we need to consider how best to gather evidence to support the watch and wait approach. Most patients prefer not to have a stoma if there is a choice. The management of rectal cancer is becoming more complex and all cases should be discussed at the colorectal MDT before any treatment is offered. All treatment options that are available should be explained to the patients and their caregivers so that genuine "shared decision making" occurs before consent for treatment is obtained[15]. Sufficient time should be given to the patient prior to making that decision. Clinicians should be aware that some patients cannot handle too much information, and provision of needed but not excessive information to these patients must be considered. However, enough information should be given so as to allow the patient to make choices that take into account their values, which can be quite different from established medical views. In cases where uncertainties exist, the patients should be encouraged to participate in ongoing clinical trials so that meaningful data can be generated to help with decision-making in the future.

Following treatment, it is sometimes difficult to assess the clinical response, especially if the clinicians are not experienced in following a watch and wait strategy. Newer cancer centers that are starting to adopt these non-surgical treatment plans should work closely with, and take advice from, more experienced clinicians at other cancer hospitals. Not all patients with mucosal abnormalities have residual tumors[8] and clinicians should be aware that not all abnormalities on MRI represent a residual tumor. There are many uncertainties and clinicians should be encouraged to work closely with oncologists at nearby cancer centers who have more experience, so as to avoid performing unnecessary salvage surgeries, which can be devastating for the patient when there is no residual cancer. Litigation could follow, and so the possibility of this scenario should be clearly explained to the patient[16]. In cases where there is clinical uncertainty, it is better to wait a little longer to clarify the situation, to determine whether or not there is regrowth of any residual tumor, as the regrowth does not progress as quickly as one would expect.

CONCLUSION

The management of rectal cancer is becoming complex, even for early-stage tumors, and all cases should be presented and discussed in an early rectal MDT. Patients have a right to refuse the MDT recommendations, and alternative treatment options should be presented and explained to the patients and their caregivers. Patients should be made aware of any uncertainties about the possible treatments, including lack of data from relevant randomized trials that might guide rational evidence-based decisions. The rectal cancer patients should be encouraged to enter into ongoing clinical trials and ongoing trials such as the Organ Preservation for Early Rectal Adenocarcinoma trial (OPERA)[17] which may provide some useful data for decision making in the future.

DECLARATIONS

Author's contributions

Both authors contributed equally to all.

Availability of data and materials

The data were strictly obtained from medical records according to the privacy policy and ethics code of our institute. All materials data are from Clatterbridge data base.

Financial support and sponsorship

None.

Conflicts of interest

Gerard JP is the medical advisor for Ariane company. Myint AS has no conflict of interest.

Ethical approval and consent to participate

Ethic approval (01-02/26). Consent was obtained in this study.

Consent for publication

Not applicable.

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Mini-invasive Surgery

Review

Open Access

The role of splenic flexure mobilization in laparoscopic rectal surgery for rectal cancer

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Abstract

Laparoscopic surgery for the treatment of colorectal cancer has gained an enormous advantage as compared to the traditional approach in terms of patient benefits. Although it has gained popularity among surgeons, there are still some contentious issues especially in laparoscopic rectal surgery. Splenic flexure mobilization is a crucial aspect of the procedure with complex technical details thereby establishing a learning curve that cannot be easily overcome. A team of colorectal surgeons at China Medical University Hospital adopted a standardized approach to laparoscopic rectal surgery particularly simplifying the steps involved in mobilizing the splenic flexure which is deemed as one of the difficult steps in the surgery.

Keywords: Splenic flexure mobilization, anterior resection, low anterior resection, laparoscopic rectal surgery

INTRODUCTION

One of the most commonly diagnosed malignancies in the world is colorectal cancer (CRC). It currently ranks third based on the GLOBOCAN (Global Cancer Incidence, Mortality and Prevalence) index and is also the fourth leading cause of cancer-related deaths. The cancer burden will be increasing by 60% to more than 2.2 million new cases and resulting in 1.1 million deaths by 2030[1]. Based on the National Cancer Registry of Taiwan, CRC is the second most common invasive neoplastic disease with a total of 15,764 cases in 2014 and a crude incidence rate of 67.27%[2]. The evolution of laparoscopic-assisted compared to open approach colorectal surgery for diverticular disease and cancer was first introduced in the early 1990s and was aimed to offer the benefit of less trauma, without compromising functional and oncological outcomes[3]. Laparoscopic surgery has gained increasing interest for the treatment of CRC. Laparoscopic approach for colon and rectal cancer was associated with less morbidity, enhanced recovery, and at least equivalent oncological outcomes[3-6]. In China Medical University Hospital (CMUH), a tertiary medical center in Taichung City, a team of colorectal surgeons performs a high volume of cases for laparoscopic rectal surgeries.

Left-sided CRC comprises two thirds of all colorectal malignancies. The standard surgical treatment is a complete oncologic resection with a primary anastomosis[7]. There were initial concerns about the potential risk of tumor cell dissemination during laparoscopy but this has not been validated. The emergence of laparoscopic colorectal surgery has not been fully embraced by most surgeons mostly because of the increased technical laparoscopic skill requirements[4]. This paper aims to discuss the importance of splenic flexure mobilization (SFM) and its technical details during laparoscopic rectal surgery.

SFM

SFM is one of the essential, challenging and technically demanding step during laparoscopic rectal cancer surgery. The use of SFM for CRC surgery remains a contentious issue[5,6,8], but safe dissection of the splenic flexure to fully mobilize the descending colon is mandatory not only for oncologic resection but also for safe anastomosis[4,9-11]. The definition of SFM is different among several studies with some describing the technique as either complete or partial mobilization[3,5,6,12]. However, it is relevant to know the procedural aspect of SFM consisting of the division of the splenocolic, phrenicocolic, gastro colic and pancreaticomesocolic ligaments. It is crucial to differentiate a partial splenic flexure from the complete SFM. In partial SFM, it is limited only to the division of splenocolic and phrenicocolic ligaments while a complete SFM includes not only the division of splenocolic and phrenicocolic ligaments (partial mobilization) but the division of gastro-colic and pancreaticomesocolic attachments. This can be technically accomplished either through a lateral-to-medial or a medial-to-lateral approach[3,4,6,9,10]. A variety of approaches for SFM have been used by surgeons to simplify the technique. A median to lateral approach for the complete mobilization of the splenic flexure was commonly described in various studies[9,10,19,20]. This approach is similar to the study of Marsden *et al.*[13], in which many surgeons favor routine mobilization of the flexure at an early stage in the operation, particularly for low rectal cancers. It is often considered helpful to carry out this step along with division of the inferior mesenteric artery (IMA), the inferior mesenteric vein (IMV) and the colon before beginning the pelvic dissection. This approach allows the divided colon and small bowel to be packed away giving good access to the pelvis for the rectal dissection[4,9,10]. This highlights the importance of a complete SFM prior to the pelvic dissection of any rectal surgery.

SFM is a crucial part in all left-sided colorectal surgeries particularly laparoscopic anterior and low anterior resections[4,9,10]. SFM is performed in order to achieve adequate oncological resection, create a tension-free anastomosis with a good blood supply, and perform a pouch reconstruction if necessary[3,4,14]. It allows to achieve a straight segment of supple and well vascularized segment of the descending colon that can be easily anastomosed to the remnant rectum down in the pelvis in which some surgeons favor creating a recreational pouch to decrease frequency of bowel movement[5]. In a cadaveric study done by Thum-umnuaysuk *et al.*[7], a greater length of colon at 17.98 ± 6.80 cm was achieved and it reached statistical significance when high ligation of IMA and IMV coupled with SFM was done. In a separate cadaveric study by Araujo *et al.*[11], it was shown that an additional 10 to 28 cm segment of the descending colon can be gained if SFM was carried out with or without distal transverse colon mobilization. Kye *et al.*[15] cited that as much as 30 centimeters of colon redundancy will be reached if high IMV ligation was performed as compared to a low IMV ligation which gains 5 centimeters less. The results in the paper of Kye *et al.*[15] had comparable results to the previous cadaveric studies which considered SFM as vital in every laparoscopic rectal surgery to come up with a lengthy colon needed to have a tension-free anastomosis. Elongation of the colon is essential in creating a tension-free anastomosis which involves adequate mobilization of the bowel ends particularly on the colonic side[16]. The vascular supply of the proximal and distal margins after resection becomes an integral part of the process[8-20]. In the process of performing a complete SFM, it is

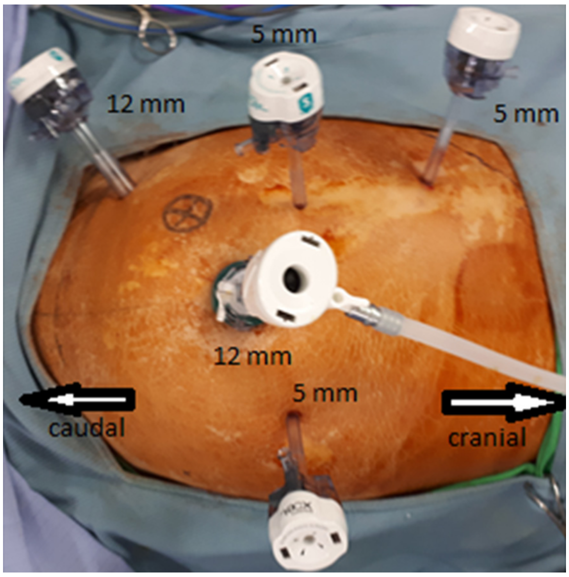

Figure 1. Placement of trocars

noteworthy that only high ligation of both the IMV and IMA as well as division of the involved attachments in the splenic flexure will result in a lengthy colon that would provide for a tension-free anastomosis. Toh *et al.*[17], highlighted the presence of an important vessel known as the Arc of Riolan that provides collateral mesenteric circulation in 10% of individuals and naturally found anterior to the IMV on the inferior border of the pancreas. It is important that this vessel should be preserved during high ligation of the IMV and splenic flexure takedown to ensure collateral supply from the SMA through the connection between the middle colic and left colic artery[17]. Performing a technically sound and complete SMF can have an impact on the patient's postoperative recovery although the success of the surgery is reliant on several compounding factors.

Several of these studies mentioned a variety of possible risk factors owing to the technical difficulty of such a procedure. The presence of comorbidities such as hypertension and diabetes mellitus, increased BMI, increased American Society of Anesthesiologist score, previous neoadjuvant chemo radiotherapy have been linked to the technical difficulty of performing SFM due to the risks that accompany it. However, the results did not reach statistical significance leading to the conclusion that the benefits of the step in all laparoscopic rectal surgeries far outweighs the risk[4-6,8-10,12,14-16]. One common intraoperative complication cited in various studies is causing tears to the spleen whether it is complete or partial avulsion will be immaterial since both can cause significant bleeding[4-6,8-10,12]. This particularly happens during the process of dividing the phrenicocolic and especially the splenocolic ligaments. There were mentions of inadvertent serosal injuries to the small bowel but they were insignificant as far as the overall result of those studies were concerned[5,12,18]. The presence of anastomotic leaks after laparoscopic rectal surgery in which SFM was performed were cited in some of the published papers[8,12,15,16,18]. It was attributed in some cases to the presence of tension and inadequate vascularity on the involved segments but no direct links were established between SFM and anastomotic leaks since it is considered to be multifactorial.

The team of colorectal surgeons in CMUH adopted the method of doing a mandatory SFM. Incorporating SFM in all laparoscopic rectal surgeries will enable the team to overcome the learning curve involved in this very technical procedure.

SURGICAL METHOD

The following part details the precise description of how a complete SFM is done in our institution. The ap-

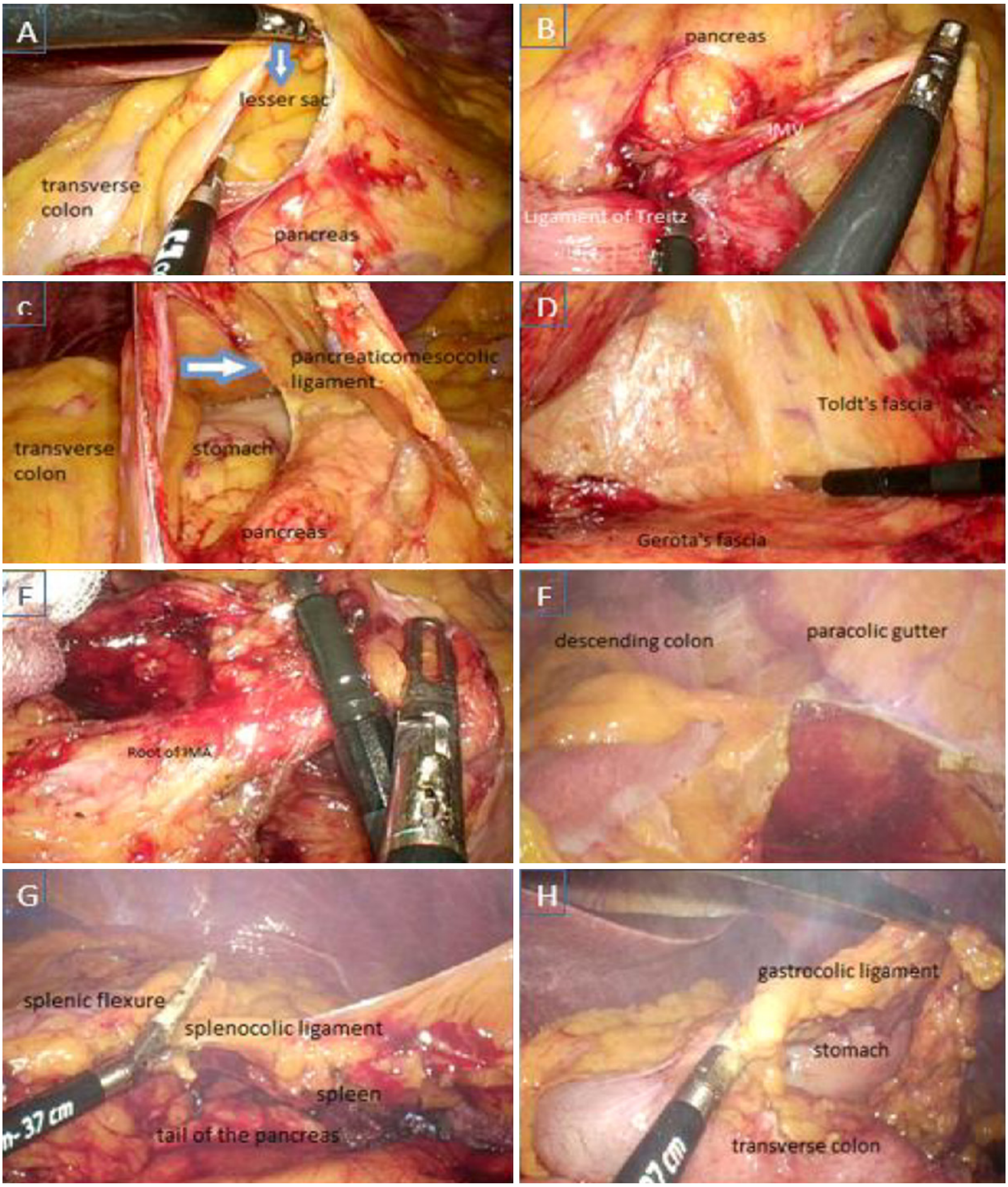

Figure 2. Splenic flexure mobilization. A: Entering the lesser sac by dividing the mesentery at the inferior border of the pancreas; B: high ligation of the inferior mesenteric vein proximal to the ligament of Treitz and on the inferior border of the pancreas; C: division of the pancreaticomesocolic ligament; D: retroperitoneal dissection and separation of the Toldt's fascia; E: ligation of the inferior mesenteric artery at its root; F: lateral dissection involving division of the left paracolic gutter; G: division of the splenocolic ligament; H: completion of splenic flexure mobilization by division of the gastrocolic ligaments

proach utilized is a combined medial to lateral and lateral to medial dissection with emphasis on the ease of performing the steps during laparoscopic surgery.

The patient is placed in a Trendelenburg and a semi-right lateral decubitus position. The patient is prepped in a conventional manner and a conventional 5-trocar placement is instituted. A 12-mm trocar is inserted at the umbilicus employing the Hasson's technique (entering the abdomen under direct visualization) as well as at the right lower quadrant of the abdomen. Additional 5 mm trocars are placed each at the right and left paraumbilical area (5-6 cm from the umbilicus) as well as on the right upper quadrant of the abdomen along the mid-clavicular line [Figure 1].

After a thorough inspection of the abdominal cavity, the small bowel is carefully placed to the right side of the abdomen using atraumatic bowel graspers and exposing the ligament of Treitz where the root of the IMV is also located. The inferior border of the pancreas is likewise identified and the mesentery is carefully grasped and sharp dissection is initiated using monopolar electro cautery to enter the lesser sac. This is followed by incising the paraaortic peritoneum and the IMV is ligated at its root and divided using *Ligasure*. The retroperitoneal dissection is carried out over the Gerota's fascia by carefully separating the Toldt's fascia aided by sharp dissection until the mesentery of the descending colon can be lifted up to form a tent. The pancreaticomesocolic attachments along the tail of the pancreas is carefully divided using Ligasure to render visible the splenic hilum [Figure 2A-D].

The IMA is identified and isolated at its take off from the abdominal aorta. The IMA is ligated at around 1-1.5 cm distal to the aorta and carefully divided using Ligasure. Posterior dissection is continued caudally while preserving all identified retroperitoneal structures along the dissection until the presacral space is reached. Sharp dissection is carried out laterally until reaching the left paracolic gutter where the parietal peritoneum commences. The sigmoid and descending colon is now mobilized by dividing the parietal peritoneum from the pelvis until the hilum of the spleen is visible. SFM is completed by detaching the omentum from the transverse colon and dividing the splenocolic and gastro colic ligaments [Figure 2E-H].

In the pelvic phase of all laparoscopic rectal surgeries, an additional 5-mm trocar can be inserted in the left lower quadrant of the abdomen that can be used by the assistant surgeon during this phase of the dissection. This is particularly done especially in low lying rectal tumors where a laparoscopic low anterior resection or transanal total mesorectal excision will be performed.

CONCLUSION

In our perspective, SFM is an integral step in performing laparoscopic surgery for rectal cancer. This will enable the surgeon to achieve a tension-free anastomosis from an adequate redundant colon and have good vascularity on both the proximal and distal ends of the segment. There is a learning curve involved in such procedure and it can easily be overcome in high volume centers such as our institution where the steps can be readily performed.

DECLARATIONS

Authors' contributions

Performed the operations: Ke TW, Geniales CR, Chen WTL
Participated in the data and patients collection, wrote the manuscript: Ke TW, Geniales CR
Supervised this study: Chen WTL

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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Mini-invasive Surgery

Original Article

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Outcomes of radical surgical management in liver hydatid cysts: 7 years center experience

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Abstract

Aim: To evaluate our experience of radical treatment in management of liver hydatid cyst. As liver is considered the organ most frequently infected with hydatid disease.

Methods: We performed a retrospective study concerning surgical management of liver hydatid cyst at Advanced Hepato-Pancreateco-Biliary Center. Our study done from June 2011 to May 2018 on 103 patients presented with hepatic hydatid cyst.

Results: Total pericystectomy was carried out in 80 (77.67%) patients; while hepatic resection was carried out in 14 (13.59%) patients. Laparoscopic management was done in 6 (5.82%) patients (5 cases with total pericystectomy and 1 case with sub-total pericystectomy and omentoplasty). Twenty-one patients developed post-operative complications, four patients suffered from biliary leak. There was no mortality. Follow-up period ranged from 6 to 60 months with no recurrence.

Conclusion: Radical surgical procedures were safe and effective in management of hepatic hydatid cyst when it was done by experienced surgeons, with lower morbidity rates and no recurrence.

Keywords: Liver hydatid cysts, pericystectomy, hepatic resection, cystobiliary communications, recurrent hydatid

INTRODUCTION

Echinococcus spp. is responsible for Hydatidosis. Accidental hosts are infected with one or more cysts in different body sites, mainly in the liver[1]. The disease is endemic in sheep rearing countries as in the

Mediterranean Sea and Middle East where there is contact with infected animals[2]. During our study, we discovered increasing incidence of liver hydatid disease. And surprisingly, we get no feedback regarding animal contact in some patients. Camels were the only contact animal in other patients.

Different management modalities were discussed before in literature, but surgery remains the standard treatment. Operative modalities range from complete resection (e.g., total pericystectomy or hepatectomy) to minimal invasive procedures (e.g., percutaneous aspiration of cysts)[3]. More recently, laparoscopic approaches take a hand in the treatment of hepatic hydatid cysts[4].

Choosing the appropriate modality for management depends on several factors: number & site of the cysts, patient general condition, type of hospital in which the surgery is performed, including the possibility of intensive postoperative care and the surgeon's expertise[5].

Radical treatment modality focuses on near total or total hepatic adventitia resection with or without hepatic parenchyma resection associated, which avoids residual cavity[6].

Here in our study, we assess our experience in radical treatment especially total pericystectomy in management of hepatic hyatid cyst.

METHODS

Patients and methods

In this retrospective study, we analyzed 103 patients with hydatid cyst managed at the Advanced Hepato-Pancreatico Biliary Center, Zagazig University Hospitals, from June 2011 till May 2018. All data as clinical, radiological, laboratory, operative, and post-operative were recorded. Comorbidity, operative morbidity and mortality, surgical procedure, length of postoperative hospital stay were also recorded.

The diagnosis was made mainly on radiological appearance (ultrasonography was the imaging of choice). In doubtful cases we also combined radiology with serology (enzyme-linked immunosorbent assay) and Triphasic CT which was used to assess location, diameter and number of cysts. We used plain x-ray chest to identify lung hyatid cyst. Magnetic resonance cholangiopancreatography (MRCP) was performed for patients with hydatid cyst more than 5 cm in diameter, recurrent and multiple cysts to assess cysto-bilary communications. Endoscopic retrograde cholangiopancreatography (ERCP) restricted to patients presented with preoperative obstructive jaundice.

Albendazole 400 mg twice daily was prescribed for two weeks prior to surgery to inactivate the organism. During the follow up period Albendazole was given with the same doses for 3 and 6 months in complicated and recurrent cases. In cirrhotic patients we reduced the dose to 200 mg twice daily for 1 week pre-operative and for 3 months postoperative.

Surgical technique

Surgeries were done by trained surgeons. Epidural catheter was used for postoperative pain management. J shaped incision "Makuuchi" was the chosen approach for good exposure. But, bilateral subcostal incision used in cases needed splenectomy. Complete liver mobilization, identification of the cyst (site and number), search for other associated cysts (intestine or kidney) followed by gauze towels soaked in hypertonic saline used to isolate the lesion and safeguard against the risk of spillage of cyst contents into the peritoneal cavity, were the routine steps.

In cases where the cyst was deep intra-parenchymal, we used intra-operative U/S to identify the proper site. Harmonic shears were used to achieve good haemostasis during liver parenchyma dissection. Also, in

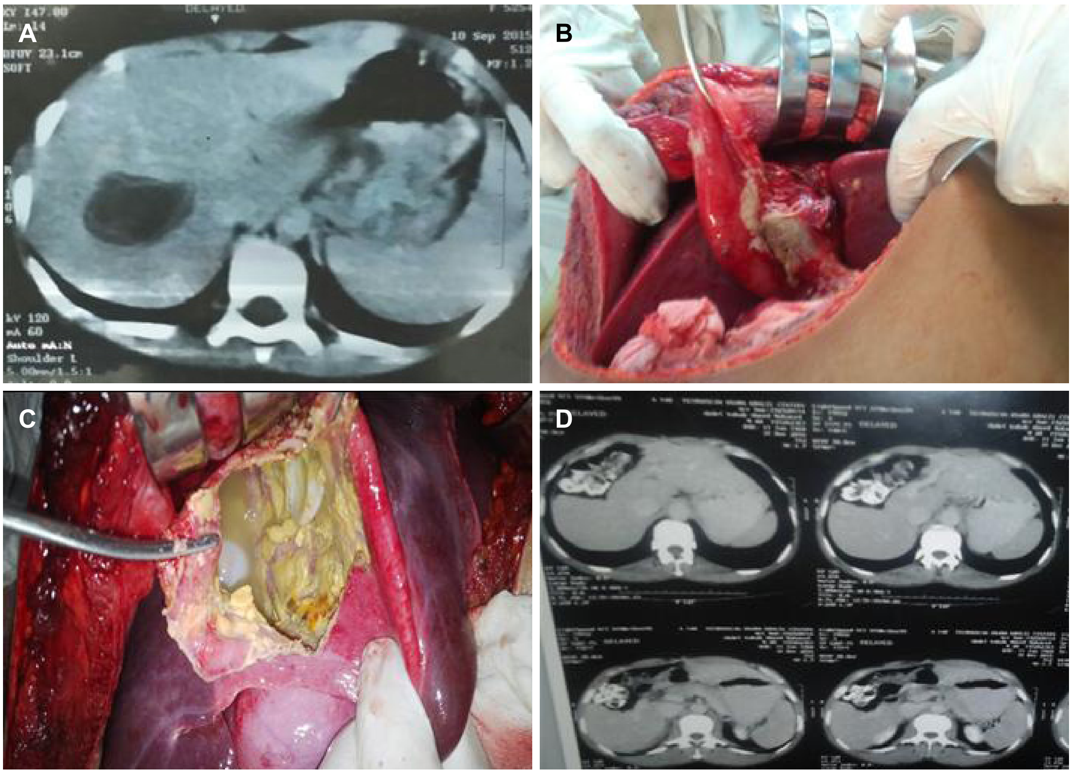

Figure 1. A: Intra-parenchymal hydatid cyst in female 9 years old; B: ruptured hydatid cyst in 17 years male; C: huge central hydatid cyst in 45 years male; D: CT 2 years after huge centeral hydatid removal

order to reduce bleeding, inflow control was done (Pringle maneuver) in some cases.

Surgical procedures were radical surgery in the form of total pericystectomy, sub-total pericystectomy and liver resection. Pericystectomy is performed with closed or open, total or sub-total method. The closed procedure was used in superficial cysts or exophytic cysts without opening the cyst. Open method was performed in deep cysts or cysts closely related to the hepatic veins or inferior vena cava (IVC). It was done by puncture of the cyst, suction of the fluid, removal of endocyst and cavity irrigation with hypertonic saline [Figure 1].

In cases of hard pericysts adherent to main vessels, especially to the IVC, we stopped dissection just before the vascular plane leaving a small part of the cyst wall (sub-total). Omentoplasty was done to prevent fluid re-accumulation and avoid recurrence.

In laparoscopic procedure, all patients were positioned in the French position and semi-left lateral position. In right side lesions, four to five ports were placed under direct visualization. A 10-mm port is placed 2-3 cm above and to the right of umbilicus for camera. Two 12-mm ports were placed about 5 cm to the left and right side of camera port and one or two 5-mm ports were placed below right and/or left costal margin for liver retraction by the assistant. In left sided lesions, the same trocars were placed in the same positions but shifted 1-2 cm to the left. Irrigation of the abdominal cavity was performed with hypertonic saline to safeguard against spillage in central cases that would underwent sub-total excision.

We sent the specimen to histopathology to confirm the diagnosis. Follow up was done at 6-60 months postoperative including physical examination, laboratory testing, ultrasonography and triphasic CT to assess the success of surgery, liver regeneration in major cases and to detect recurrence.

RESULTS

Our study included 103 patients with hydatid disease. 32 (31.068%) were males and 71 were (68.932%) females. The median age at presentation was 35 (range 10-65) years. 65 (63.11%) patients presented with symptoms. The most common symptom was abdominal pain presented in all symptomatic patients. Serology test was positive in 76 (73.79%) patients. Ultrasound was positive in all patients.

Cyst was solitary in 74 (71.84%) cases. The most common size of the cyst was 7-10 cm presented in 62 (60.19%) patients. Huge cyst more than 20 cm was found in 4 patients. Most of the cysts were in the right lobe 69 (66.99%) cases. A total of 76 (73.79%) patients had deep cysts [Table 1].

We faced complicated cysts in 30 patients, as well as ruptured cysts in 3 patients (25 years male patient with ruptured cyst inside the CBD, 17 years male patient with ruptured central hydatid cyst discovered incidentally during operation, which was at the area of the porta-hepatis and 35 years female patient with ruptured cyst at segment IV discovered incidentally during operation). Infected cysts were found in 12 patients (7 of them were due to percutaneous ultrasound (US) guided diagnostic aspiration fine needle aspiration cytopathology).

We also managed recurrent cysts in 15 cases (4 M & 11 F); 7 cases with past history of US guided drainage and 8 cases with past history of conservative surgery (endocystectomy). Two patients after US guided aspiration had more than 1 cyst; 1 male patient had 3 cysts (1 huge in the peritoneum, 1 in the liver and 1 in the spleen) and 1 female with 2 cysts in the left lobe. Two females also after endocystectomy had more than 1 cyst; 1 with 3 cysts (2 of them were biliary cyst) and the other one had 2 cysts 1 in the left lobe and 1 in the right lobe [Table 2].

Total pericystectomy was carried out on 80 (77.67%) patients [open method in 49 (47.57%) patients and closed method in 31 (30.1%) patients]. Hepatic resection was carried out on 14 (13.59%) patients and 3 (4.3%) patients required a subtotal pericystectomy with omentoplasty (where the IVC and hepatic veins forming the posterior wall of the cyst).

Laparoscopic management used in 6 (5.82%) patients (laparoscopic total pericystectomy in 5 cases and laparoscopic subtotal pericystectomy and omentoplasty in one patient).

Intra-operative US was done in 4 patients in whom the cyst was totally intra-parenchymal and not palpable. Intra-operative cholangiography done in 9 patients. While intra-operative ERCP and stenting was done in one female patient, that had huge cyst including CBD. Cysto-biliary communications were found in 78 (82.6%) patients. Major communications were found in 42 (40.78%) patients. However minor cysto-biliary communications were presented in 36 (34.95%) patients.

The mean operative time was 170 min. The average intra-operative blood loss was less than 600 mL. Thirty-two patients needed packed RBCs transfusion while 39 patients needed FFP transfusion. The mean hospital stay was 7 days in all patients. The mean ICU stay was 2 days in 18 (17.48%) patients.

Twenty-one (20.39%) patients developed post-operative complications with no mortality or recurrence. Postoperative bleeding occurred in female patient after 10 h post operatively which re-explored (bleeding was from liver bed and slipped ligature from one of the varices at the splenic bed).

Four patients developed post-operative bile leaks (one of them with right hepatectomy, biloma was at the cut-surface that needed percutaneous US guided pigtail catheter drainage, removed after 2 weeks. The other 3 were managed conservatively).

Table 1. Characters of the hepatic hydatid cyst

Characters	Number
Type	
Clear	29 (38.16%)
Multivesicular	74 (71.84%)
Size	
≤ 6 cm	22 (21.36%)
7-10 cm	62 (60.19%)
11-20 cm	15 (14.56%)
> 20 cm	4 (3.89%)
Cyst number	
One cyst	74 (71.84%)
Two cysts	19 (18.44%)
More than 2 cysts	10 (9.72%)
Associations	14 (13.59%)
CBD	2 (1.94%)
Spleen	10 (9.71%)
Peritoneum	2 (1.94%)
Location	
RT lobe	69 (66.99%)
Whole	4 (3.88%)
RT. Post Seg. VI, VII	17 (16.5%)
RT. Ant Seg. V, VIII	6 (5.82%)
Segment V	8 (7.77%)
Segment VI	18 (17.48%)
Segment VII	9 (8.74%)
Segment VIII	7 (7.8%)
LT lobe	21 (20.39%)
LT Lat. Seg. II, III	16 (15.53%)
Segment IV	5 (4.86%)
Central liver	
Segment IV, V, VIII	4 (3.88%)
Bilobar	9 (8.74%)
Site	
Superficial	27 (26.21%)
Vasculo-biliary cyst	76 (73.79%)
Non-complicated	73 (70.87%)
Complicated cysts before surgery	30 (29.13%)
Rupture	3 (2.91%)
Infection	12 (11.65%)
Recurrence	15 (14.56%)
Complicated cysts After US guided drainage	7 (6.8%)
Complicated cysts After endo-cystectomy	8 (7.76%)

Eight patients developed right sided pleural effusion, managed by albumin and diuretics. Four patients developed ascites due to liver cirrhosis and portal hypertension were also managed by albumin and diuretics. We faced wound infection in 5 patients. While incisional hernia in 3 patients developed 1 year after surgery [Table 3].

DISCUSSION

Hydatid disease increased in sheep raising areas[7]. The increased number of people immigrated from contaminated areas as Iraq and Syria because of war as well as dogs in the street and contamination of vegetables with dogs' excreta, enhance the incidence of hydatid disease in our country lately.

The hydatid cyst presentation is always asymptomatic for many years, as it enlarges slowly[8]. In our series, 38 (36.89%) patients were asymptomatic at the time of diagnosis. Symptoms arise either from pressure effects on adjacent organs or when a complication occurs[9]. The sensitivity of US in liver hydatid disease diagnosis was 100%. Affection of liver lobes by Hydatid disease was more in the right lobe[10], which was matching with our patients 69 (66.99%). The cysts are more commonly solitary as was the case in 74 (71.84%) of our patients.

Table 2. Characters of recurrent cases managed by total pericystectomy

N	Demographic data				Cyst characters			
	Age	Sex	Symptoms	Co-morbidity	No.	Size	Location	Associations
Seven cases with past history of US guided drainage								
1	55	M	Abdominal pain Mass	HPN	3	Peritoneum > 20 cm Spleen 8 cm × 7 cm Liver 6 cm × 6 cm	Seg. II, III	Peritoneum Spleen
2	22	F	Abdominal pain	Non	1	7 cm × 7 cm	Seg. VIII	Non
3	35	F	Abdominal pain Nausea & Vomiting	Non	1	8 cm × 8 cm	Seg. V	GB stones
4	28	M	Abdominal pain	Liver cirrhosis HCV + ve	1	6 cm × 7 cm	Seg. VI	Non
5	30	F	Abdominal pain	Non	1	8 cm × 8 cm	Seg. II, III	Non
6	35	F	Abdominal pain	Non	1	7 cm × 7 cm	Seg. VII	Non
7	48	F	Abdominal pain Fever	Cardiac	2	6 cm × 7 cm 3 cm × 3 cm	Seg. III, III	Non
Eight cases with past history of endocystectomy								
1	23	F	Abdominal pain	Non	1	7 cm × 8 cm	Seg. VII	Biliary Fistula
2	32	F	Abdominal pain	Non	1	7 cm × 6 cm	Seg. VI	Non
3	25	F	Abdominal pain Nausea & Vomiting	Non	1	8 cm × 8 cm	Seg. VIII	Non
4	50	F	Incisional hernia Abdominal pain	Non	3	RT 9 cm × 8 cm 7 cm × 7 cm LT 6 cm × 5 cm	2 RT Seg. VIII Seg. VI 1 LT Seg.IV	Past history of splenectomy Right biliary cyst after endocystectomy
5	45	M	Abdominal pain	DM	1	7 cm × 8 cm	Seg. IV	Non
6	28	F	Abdominal pain Nausea & Vomiting	Non	1	6 cm × 8 cm	Seg. II, III	GB stones
7	27	F	Abdominal pain	Non	2	LT 6 cm × 6 cm RT 7 cm × 8 cm	LT Seg. IV RT Seg. VII	Non
8	55	M	Abdominal pain	HCV + ve	1	8 cm × 9 cm	Seg II, III	Biliary Fistula

Table 3. Postoperative outcomes

Outcome		Number
Hospital stay	7 days (5-10 days)	
ICU stay	2 days (1-3 days)	18 (17.48%)
Operative time	170 min (120-250 min)	
Blood loss	600 mL (300-2000 mL)	
Blood transfusion	2-4 units	32 (31.07%)
Fresh frozen plasma	2-4 units	39 (37.86%)
Complications[1]		21 (20.39%)
Bleeding		1 (0.97%)
Biliary leak		4 (3.88%)
Chest infection		4 (3.88%)
Pleural effusion		8 (7.76%)
Ascites		4 (3.88%)
Wound infection		5 (4.85%)
Burst abdomen		1 (0.97%)
Incisional hernia		3 (2.91%)

[1]Patient had more than one complication

Assessment of cysto-biliary communication presence via preoperative detection was essential. Recurrent episodes of cholangitis and Large cysts occupying several liver segments are highly suggestive of cysto-biliary communications, and a search for the fistula should be meticulous[11]. In our series MRCP was mandatory for all patients for detection of cysto-biliary communications.

Since effective anti-parasitic medical treatment has not yet proved to treat and to effectively cure the disease, the optimal treatment for hepatic hydatid cyst is surgery[12]. Treatment of hepatic hydatid cyst should be focused on parasite elimination, and treatment of both the adventitia as well as the cavity.

Total or near total pericystectomy is the chosen treatment for hepatic hydatid cyst, because it is the only management modality that treats the disease integrally with low morbidity and mortality[13]. If we don't resect the infected adventitia well, which is known to contain exogenous vesicles, that may lead to relapse of the disease. Due to this reason radical treatment prevents residual cavity disease and thus prevents relapse[9,13]. In our study, radical procedure was done in 96.12% of the patients (liver resection in 14.59%, total pericystectomy in 77.67% and laparoscopic total pericystectomy in 4.85%). In a study of Marco *et al.*[6], a radical treatment was performed for 93%, and for 81% of these patients, total or near total cystectomy was done.

In addition to ordinary open surgical techniques, the laparoscopic approach has been used as a new modality for hydatid cyst treatment.

The laparoscopic approach on open approach affords a short hospital stay, less invasiveness, lower incidence of wound infection and less postoperative pain[14]. Disadvantages of laparoscopic technique are limited manipulation, difficult thick viscous content aspirating, increased risk of cyst content spillage and the difficult approach deeply-seated lesions[15]. Note that centrally located cysts carry a high risk of bleeding, so we should think in conventional open method, for its management[16].

Radical hydatid cyst treatment showed better results and low risk for complications[17]. In our study, the average intra-operative bleeding was less than 600 mL, ranging from 300 mL to 2000 mL. About 31.07% of the patients required an intraoperative blood transfusion. Less than 20% of the patients required hospitalization in ICU during the first 24 h postoperatively.

Complicated hydatid liver cysts was found in 15% to 60% of patients at the time of diagnosis[18]. We managed 30 (29.13%) patients with complicated hydatid cyst. The most important cases were the 8 cases that recurrent after incomplete resection (endocystectomy and drainage). Three of the cases were presented with biliary complications (1 with biliary cyst and 2 with biliary fistula).

The type of surgery: either conservative method (deroofing, drainage) or radical surgery (pericystectomy and hepatectomy) is the major factor for hydatid cyst recurrence[18]. Aydin *et al.*[19] comparative retrospective study on 242 patients described significantly higher morbidity and recurrence rates in patients managed by conservative surgery (11% *vs.* 3%; 24% *vs.* 3%). In another study by Tagliacozzo *et al.*[20], from 454 patients, 214 were managed with conservative surgery (external drainage, marsupialization or omentoplasty), while the remaining 240 managed with radical surgery. Morbidity and recurrence rates were significantly higher in the group that was managed conservatively. In our study no recurrence was detected during the follow up period.

Biliary leakage and fistulas are the main immediate post-operative complications after conservative procedures, beside septic complications of the residual cavity. A pericyst left in situ (especially if thick and calcified) represents two major obstacles. First, delay liver regeneration filling the residual cavity, leading to serum and blood accumulation or liver abscess formation. Second, pericyst persistence may hide possible biliary communication in the residual cavity leading to biliary fistula, which occurs in up to 50% of patients after conservative managemenet[3].

However radical procedure advantages in this particular issue allow exact detection and safe suture of biliary and vascular branches in the healthy parenchyma which definitely reduce the risk of biliary leak and blood collection. Spontaneous reduction of the residual cavity by liver regeneration would happen[21].

Albendazole may play a role to prevent recurrences after surgery using 400 mg twice daily for 3-6 months.

According to the WHO, antiparasitic chemotherapy treatment is considered an important indication to prevent secondary echinococcosis and reduce the risk of recurrence. In patients who didn't take albendazole, recurrence rate was 18.75%, compared to 4.16% recurrence rate in patients who received albendazole therapy[22]. In our study, we give the patients albendazole 400 mg twice daily for 1-2 weeks before surgery, and postoperative for 3 months in uncomplicated cases and 6 months for complicated cases.

In conclusion, pericystectomy is a safe and effective management modality for liver hydatid cyst either complicated or uncomplicated. This attributed to no mortality, less morbidity and no recurrence especially when done by experienced surgeons and specialized centers with appropriate equipment.

DECLARATIONS

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Authors' contributions

Design, literature research, data acquisition, drafted manuscript: Mansy W, Mohamed M, Saber S
Data analysis: Mohamed M
Revised manuscript: Mansy W

Availability of data and materials

Patients were identified using Advanced Hepato-Pancreateco-Biliary Center database. Data were collected retrospectively through systematic review of patient charts and imaging. The de-identified data is available by contacting the corresponding author Associate Professor wael mansy.

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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Mini-invasive Surgery

Review

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Surgical management of hereditary colorectal cancer

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Abstract
Colorectal cancer (CRC) is one of the most common solid malignancies worldwide. Although sporadic CRC represents the most common form, genetic alterations is increasingly being identified in a relevant portion of patients with CRC. Familial CRC describes an increased incidence of adenomatous polyps and CRC in first - degree relatives. Hereditary CRC is defined by the identification of deleterious mutations in known predisposing genes. Typical hereditary syndromes with predisposition to CRC include: hereditary non-polyposis colon cancer or Lynch syndrome, familial adenomatous polyposis, attenuated familial adenomatous polyposis, Peutz-Jeghers syndrome and *MUTYH* associated polyposis. Newly identified genetic alterations with increased risk for CRC include: *PPAP*, *NAD*, *MSH3* and *NTHL1*. The diagnosis, surveillance and optimal surgical management of patients with hereditary predisposition to CRC warrant a good understanding of the genetic syndrome in question. Prophylactic surgery must be segregated from symptom-related procedures depending on the syndrome in question. The need for extended surgical procedures must be made in an individualized manner based on gene and gender. The patient should play an active role in the surgical decision-making. Minimally invasive access should be the preferred approach and postoperative quality of life must be seen as a primary outcome measure.

Keywords: Hereditary colorectal cancer, hereditary non-polyposis colon cancer, Lynch Syndrome, familial adenomatous polyposis, *MUTYH* associated polyposis, polyposis, proctocolectomy, virtual ileostomy

INTRODUCTION

Colorectal cancer (CRC) represents one of the most common solid malignancies worldwide[1]. Based on the underlying pathogenesis, three distinct groups of CRC can be identified. Sporadic CRC is usually diagnosed in individuals aged 50 years and above and represents approximately 60%-70% of CRC and is as such the most common entity. These patients by definition do not harbor a deleterious predisposing hereditary mutation[2].

The second group has been termed, familial colorectal cancer and describes families with an increased incidence of CRC. Typically, CRC has been diagnosed in more than one close relative. By definition this applies when a first - degree relative (parent, sibling or child) has been diagnosed with CRC[3]. Screening colonoscopy is recommended for the relatives at risk beginning at the age of 40 or 10 years before the youngest age of onset in the family. This group has been reported to account for about 20%-30% of all CRC[3].

The third group includes cases with hereditary CRC, due to a single deleterious mutation in one of the known predisposing genes. Based on multiple mutational abnormalities in different organ systems and additionally a heterogenous phenotype, these mutational pathologies are best summarized as syndromes, which are defined based on clinical, histopathological and genetic findings. With advances in genetic research, it is expected that many more genes involved in predisposition to cancer will be identified in affected individuals.

Well studied hereditary syndromes with predisposition to CRC currently include: hereditary non-polyposis colon cancer (HNPCC) or Lynch syndrome (LS), familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (aFAP), Peutz-Jeghers syndrome (PJS) and *MUTYH* associated polyposis (MAP)[4,5]. Recently described inheritable genetic alterations with increased risk for CRC further include polymerase proofreading associated polyposis (*PPAP*), *NAD*, *MSH3* and *NTH* like DNA glycosylase 1 (*NTHL1*)[5]. All these hereditary syndromes do not only vary widely in terms of clinical presentation but individually present with variable risks of CRC and also involvement of additional benign and malignant neoplastic growth. Interestingly, intrafamilial heterogeneity is common, despite the fact that the affected harbor the identical deleterious mutation. This is an indication of the influence of modifying genetic and epigenetic factors.

The surgical management of patients with hereditary CRC warrants identification and an understanding of the underlying syndrome. The heterogeneity of the phenotype, risk of organ-specific malignant transformation and the quality of life following surgery amongst others must be taken into consideration and discussed at the time of CRC ideally prior to surgery. A personalized approach should always be considered to offer each individual patient the best management option based on gene and gender and the estimated risk, depending on available evidence. However, patient preference is important and the explanation of risk can be challenging.

This review focuses on hereditary syndromes with predisposition to CRC. The most relevant syndromes will be addressed with focus on surgical considerations regarding oncological and functional outcome.

HNPCC (LS)

LS describes a wide spectrum of clinical findings with a high risk of gastrointestinal, urinary and gynecological cancers[6,7]. The underlying pathology is related to defective mismatch repair (*MMR*) genes, which are associated with a high level of microstatellite instability (MSI-H). These germline mutations are autosomal dominantly transmitted and thus carry a 50% risk of inheritance[8]. The identification of a pathogenic germline *MMR* mutation (and implicitly a MSI-H tumor phenotype) defines LS[8]. HNPCC is the clinical colorectal manifestation following the familial pattern of inheritance as described in the clinical pattern of the Bethesda or Amsterdam criteria, whereas LS is attributed to an individual with a pathogenic mutation in one of the *MMR* genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*).

LS is often associated with a young age of onset and is accountable for 3%-5% of CRC with a predominance

Table 1. Amsterdam II criteria and revised Bethesda criteria

Type	Description
Amsterdam II criteria	1. Three or more relative with a Lynch - associated malignancy (gastrointestinal cancers,endometrial cancer, ureter or renal pelvic cancer) 2. Two or more successive generations involved including involvement of a first-degree relative 3. At one individual is diagnosed before the age of 50 years 4. Familial adenomatous polyposis has been ruled out
Revised Bethesda criteria	1. Colorectal cancer diagnosed in a patient less than 50 years of age 2. Synchronous or metachronous colorectal cancer or other Lynch tumor independent of age 3. Colorectal cancer with MSI-H diagnosed in a patient less than 60 years of age 4. Colorectal cancer diagnosed in one or more first-degree relative with a Lynch-related tumor, one of which is diagnosed on or before the age of 50 years 5. Colorectal cancer diagnosed in two or more first or second-degree relativen with Lnych-related tumors regardless of age

MSI-H: high level of microstatellite instability

in the proximal colon. However, both old age and left-sided or rectal cancers are far more frequent than originally described, since more systematic detection and a more unbiased approach have been pursued. Histopathologically, HNPCC tumors are usually large, mutinous, poorly differentiated and exhibit an extensive lymphocytic infiltration[9]. Despite these unfavorable histopathological features, HNPCC tumors rarely metastasize and are therefore associated with a better prognosis compared to sporadic CRC[10].

The clinical diagnosis of HNPCC is based on the patient's personal and family history. The Amsterdarm II criteria[11] and the revised Bethesda criteria[12] [Table 1] still remain the most common approach for identifying potential Lynch patients or families, despite their poor sensitivity and specificity. Histopathologic examination of tumor biopsies obtained during colonoscopy including immunohistochemical staining for gene products of the *MMR* genes represents a simple and cost-effective method of identifying individuals with *MMR* deficiency requiring an individualized therapeutic approach. Of these, approximately 30% will harbour a constitutional mutation, that leads to the diagnosis LS[13]. Therefore all patients with the substantial family history and/or *MMR* deficiency in the tumor (biopsy) require genetic counseling and if consented genetic testing in a DNA sample in normal tissue.

Recently, it has been demonstrated that systematic tumor testing without previous staining for loss of protein expression renders a more efficient approach. The authors conclude that "up-front tumor sequencing in colorectal cancer is simpler and has superior sensitivity to current multitest approaches to Lynch syndrome screening, while simultaneously providing critical information for treatment selection"[14]. Also, germline testing in unselected CRC cases with a gene panel [25 known predisposing genes for gastrointestinal tract (GI) cancers] rendered a yield of nearly 10% of identified carriers with a pathogenic mutation. These recent results indicate the need to reassess the value of systematic panel testing either in the tumor or in constitutional DNA as a preferred method for identification of patients with hereditary conditions, rather than staining for *MMR* deficiency, also taking into account that the polyposis syndromes are almost all stable (exception PPAP and MSH3 polyposis). Specifically for a tailored surgical approach, it is of increasing importance to be aware of the risk disposition for subsequent cancers.

Individuals with a confirmed pathogenic mutation benefit from a regular surveillance program, although the value of each screening procedure must be weighed against potential harm and to date there is a lack of evidence for some of the recommendations. Also, there is no global agreement on the intervals and type of procedures or quality assurance. Beside this, additional data has evolved indicating that a more differentiated approach on the basis of the different *MMR* genes and gender is required[15].

The indications for colorectal surgery in patients with HNPCC are basically similar to those in patients with sporadic CRC. Premalignant polyps with severe dysplasia, large polyps not amendable via colonoscopy and malignancy represent the most common indications for surgery. LS, in contrast to familial polyposis (FAP) is not associated with full penetrance, therefore prophylactic colorectal resection is not generally recommended. However, the indication for surgery can be extended in selected cases as personalized decision-making based on gene and gender[16-18]. A personalized option might include a combination of (sub)total colectomy in place of the indicated oncological segmental resection at the time of a first CRC in combination with a purely prophylactic hysterectomy with or without adnectomy in a female with LS after completion of family planning.

Surgical management of histologically confirmed LS-associated CRC as a minimal requirement should be in accordance with current oncologic standards. Therefore colon cancer should be managed via colectomy (right or left) without compromise in the oncological thoroughness, despite the observed better prognosis of *MMR*-deficient tumors. Possibly, complete mesocolic excision (CME) as described by Hohenberger *et al.*[19] may as is suggested for sporadic cancer demonstrate superiority - this evidence is as of yet not demonstrated. In accordance, cancer of the proximal rectum or rectosigmoid junction should be managed with anterior rectal resection and partial mesorectal excision, whilest mid and low rectal cancers are managed with total mesorectal excision as described by Heald *et al.*[20]. However, it is mandatory to discuss with patients a prophylactically extended option of additional removal of the colorectum as an alternative to segmental procedures and regular colonoscopies.

The benefits of the laparoscopic approach are well documented for oncological conditions which represent the preferred means of access[21]. For cancer of the mid and lower rectum the transanal total mesorectal excision (taTME) is of increasing importance due to suggested advantages with regard to identification and preservation of pelvic nerves[22,23].

FAP

FAP is the second most common monogenetic hereditary syndrome with predisposition to CRC. FAP is caused by germline mutations of the tumor suppressor *APC*-gene on chromosome 22q21-22 involving over 2800 codons[24]. The prevalence of this syndrome has been estimated at 1 in 10,000 individuals with the spectrum of clinical presentation depending largely on the mutated codons[25]. Clinically, classical FAP can be distinguished from an attenuated variant (aFAP)[26]. Both conditions are caused by mutations in the same gene, which are allocated to different coding regions.

Classically, FAP is characterized by the development of hundreds to thousands of colonic polyps (adenomas) early in the adolescence[27]. Unlike many other hereditary syndromes with predisposition to CRC, FAP has a one hundred percent penetrance with regard to the development of CRC[28]. Therefore, FAP patients would inevitably develop CRC usually before the age of 40 years if left untreated. More so, close to 13% of FAP patients develop CRC by the age of 25 and about 95% would have developed CRC by the age of 50 years[29].

The attenuated form of FAP (aFAP) is clinically characterized by a later onset on colonic polyposis after ten years compared to cases with classical FAP[30]. Besides, individuals with aFAP present with a significant fewer amount of polyps, usually tens to a few hundreds, mostly in the proximal colon. Unlike FAP, aFAP is not associated with a complete penetrance for CRC. The lifetime risk of CRC in aFAP is estimated at about 70%[31].

FAP (and aFAP) are not only limited to the colon. Extra-colonic manifestations are very common since the germline mutations can affect virtually every organ[32]. Current genetic studies, have identified formerly defined syndromes like Gardner syndrome characterized by FAP, epidermoid cysts, osteomas, desmoid tumors and dental anomalities as merely some aspects of presentation of FAP syndrome[33]. Equally, polyposis of the upper GI is common in FAP patients. Duodenal polyps for example dependent of patient's age, occur in almost 90% of FAP patients and duodenal cancer is the second most common malignancy in FAP patients[34].

The diagnosis of FAP (aFAP) is usually straight forward. Identifying multiple, up to hundreds of polyps on colonoscopy in an individual with a family history of FAP is de facto the actionable phenotype. Alongside, the presence of extra-colonic manifestations e.g. osteomas, congenital hypertrophy of the retinal pigment epithelium, *etc.* are indicative of FAP. *APC* mutation analysis by genetic testing would confirm the suspected diagnosis. However, increasingly rarer heritable syndromes are clinically indistinguishable regarding the colorectal phenotype. In order to adequately judge the risks, it is increasingly important to identify the underlying gene, as demonstrated by gene panel testing with surprising results. This is leading to a shift in paradigm regarding our clinical ability to identify hereditary predispositions to cancer.

Individuals with genetically confirmed FAP as well as individuals at risk should undergo endoscopic surveillance every 1-2 years. The recommended surveillance frequency increases to once per year as soon as adenomatous polyps appear. This interval stays until surgical management via proctocolectomy (colectomy for aFAP) is performed and is further warranted for manifestations in other organs[35].

Generally accepted indications for surgical management include large adenomas > 1 cm, numerous adenomas (> 20), unfavorable histology (high grade dysplasia or carcinoma), chronic anemia and failure to thrive. Otherwise, surgical management is performed in a personalized manner, usually if possible postponed until after puberty[36].

Restorative proctocolectomy with an ileal pouch anal anastomosis (IPAA) is the recommended treatment for classical FAP. The vulnerable colon and rectum are removed leaving a 2 cm sensitive rectal cuff (transition zone) above the anus for solid-liquid-gas discrimination[37]. The rectal mucosal cuff, however, must be seen as a risky island with a residual risk of mucosal dysplasia as high as 4.5% after 10 years follow-up[38]. Thus the need for a stringent endoscopic follow-up cannot be over emphasized. Some surgeons perform a mucosectomy during IPAA with the goal of preventing future rectal cuff cancer although poor functionality has been reported following mucosectomy[39]. This has been attributed primarily to loss of the sensitive transitional zone and secondary to injury of the sphincter apparatus during dissection. We perform mucosectomy in selected cases when the transitional zone is involved in the disease process at the time of primary surgery. Also, the recurrence rate of neoplasia following primary mucosectomy remains high and may be repeated. For this reason at our institution we have also implemented the taTME approach for benign disease. By performing a double purse-string anastomosis at the height of the dentate line the rectal remnant and all mucosa is eliminated, it may be expected that this will further reduce the neoplastic changes seen today in the ageing FAP population with a rectal remnant of (at least) 2 cm. Functional results in this small series, to date are excellent but require prospective documentation.

Preserving the rectum and it's reservoir function via a colectomy with an ileorectal anastomosis is also an established option in most aFAP individuals. This option is open to individuals with little or no rectal polyposis. The advantages of the ileorectal anastomosis include a reduced number of bowel movements, a better continence and potentially a better quality of life compared to IPAA, although this has not been proven[40]. However, such patients need to be closely monitored (annually initially, then in 4-6 monthly intervals after the age of 50) via endoscopy of the disposed rectal remnant. Subtotal colectomy with ileosigmoid anastomosis should be considered in individuals with aFAP with polyposis of the proximal colon. These options should be considered in the attenuated FAP phenotype and especially in female patients of reproductive age to avoid pelvic dissection and formation of adhesions.

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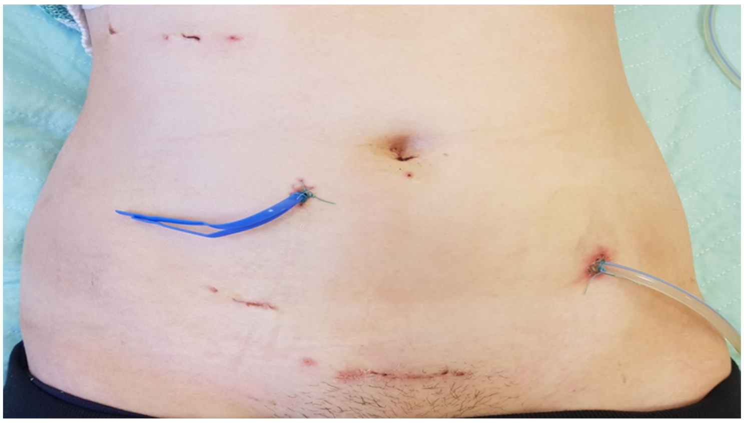

Figure 1. Virtual ileostomy with an exteriorized blue vassel loop following ileal pouch anal anastomosis for familial adenomatous polyposis

Surgical management of individuals with FAP (and aFAP) should preferably be done via minimally invasive access. Laparoscopic colectomy and proctocolectomy now represent standard procedures for FAP patients. An increasing number of FAP patients are developing desmoid tumors[41]. These fibrous tumors are considered to be triggered by trauma, including surgical trauma. Thus reducing surgical trauma via laparoscopic access should be a primary goal in these patients. This is also true with regard to the creation of a diverting ileostomy during IPAA. Ileostomy creation and eventually reversal contribute to significant surgical trauma with an increased risk of desmoid tumor. We routinely use a virtual ileostomy (ghost ileostomy) [Figure 1] during IPAA for FAP instead of a diverting ileostomy[42].

A majority of patients undergoing prophylactic proctocolectomy with FAP have no evidence of cancer. Therefore, oncologic dissection must not be performed in these patients. However, we prefer central dissection of the mesentery for three reasons: first central dissection with CME is standard for oncologic segmental colectomy. We therefore have expertise in this dissection, which is time-sparing with less vessel ligations required. Second, there is a possibility that cancer might be found in the surgical specimen for which oncologic resection would have been indicated. Thus a preemptive oncologic resection is sensible. Third, the mesenteric remnant is a predisposing site for the development of desmoid tumors [Figure 2]. In this light, pelvic dissection should be performed in accordance with TME because desmoid tumors in the remaining rectal mesentery may later impair pouch functionality. These surgical aspects are of utmost importance because desmoid tumors comprise the second most common cause of death after cancer in patients with FAP and are the most relevant factor deteriorating the quality of life in FAP patients.

Patients undergong (prophylactic) restorative proctocolectomy with IPAA for FAP are usually young and active. Therefore, quality of life is a central outcome measure in these patients. Key parameters in this regard are the number of bowel movements and fecal continence. The continent function depends mainly on the stool consistency, but also on the intactness of both the sphincter apparatus and the pelvic nerves. The identification and preservation of these nerves could be difficult via the top - bottom dissection during laparoscopic surgery. TaTME is now an established method in the management of mid and low rectal cancer[43]. This technique is a further modification of transanal minimally invasive techniques and enables a bottom - top dissection with improved visualization of the pelvic nerves and a rendezvous-approach. TaTME now represents our standard procedure for pelvic dissection during proctocolectomy[44].

The anastomosis technique for IPAA remains an issue of controversial debate. The most common anastomosis techniques include the double purse - string with single stapling, double stapling and the hand-sewn anastomosis. The double stapling technique is easy to perform. However, stapler intersection might pre-

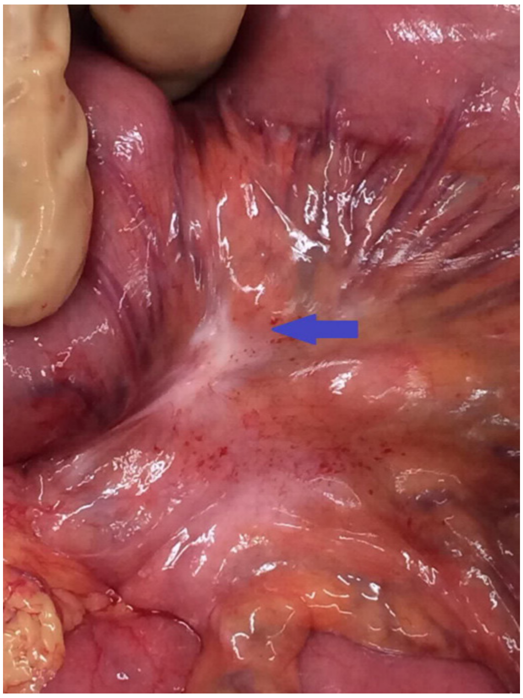

Figure 2. The arrow indicates a desmoid plaque of the small bowel mesenterium

dispose to anastomotic dehiscence, which is the most severe complication following IPAA. The hand-sewn anastomosis can be challenging and demanding in unexperienced hands. Continence function has been shown to be better following double stapling in comparison to hand-sewn anastomosis[45].

The single - stapling technique following double purse-string is our preferred technique for IPAA. Outcomes with this technique are similar to the double-stapled technique. A major advantage of the single stapled anastomosis is the lack of interposition of staplers predisposing to anastomotic dehiscence.

The need of a diverting ileostomy in patients undergoing IPAA for FAP remains a point of controversy. FAP patients are usually young and otherwise healthy with no risk factors for anastomotic leakage[46]. The rate of anastomotic leakage as high as 10% has been reported in this population[47]. Due to the fear of devastating consequences following anastomotic leakage, some surgeons prefer to perform fecal diversion during IPAA. We generally do not routinely use a diverting ileostomy during IPAA. Instead we use a virtual ileostomy [Figure 1], which can be easily converted to a defunctional ileostomy in case of a clinically relevant anastomotic leakage[42]. We complete the procedure with the placement of a transanal decompression tube [Figure 3].

MAP

MAP is caused by biallelic mutations in the *MUTYH* (myh) gene. The *MUTYH* gene is involved in base excision repair in the set-up of oxidative DNA damage by preventing G:C to T:A transversions[48]. Unlike monoallelic mutations with predisposition to CRC with an autosomal dominant transmission, siblings of biallelic *MUTYH* mutations have a 25% chance of having MAP. This is based on the autosomal recessive transmission pattern, indicating that parents and children of affected individuals are usually not affected[49].

The clinical presentation in MAP is similar to that of aFAP, with tens to hundreds of polyps with proximal colonic predominance by the age of 40-45 years found during colonoscopy[50]. Although adenomatous polyps predominate, hyperplasic polyps are common in MAP[51]. This is a major distinguishing histologic feature.

Figure 3. Placement of a transanal decompression tube into the ileal pouch at the end of ileal pouch anal anastomosis

Genetic testing for MAP is recommended in patients with clinical features of FAP or aFAP without identifiable *APC* mutation. The gene is included in all gene panels for hereditary GI predisposition and is not infrequent in this setting.

Colonoscopic surveillance is recommended in individuals with MAP typically starting in their mid-20's. There is no indication for prophylactic surgery without neoplastic changes. Subtotal colectomy is the procedure of choice in MAP patients with CRC or severe dysplasia or a high polyp burden. Relative indications for surgery include troublesome colonoscopy or the situations when polyps become too large to be removed endoscopically.

HAMARTOMATOUS POLYPOSIS SYNDROMES

Peutz-jeghers syndrome (PJS) is a genetic syndrome associated with hamartomatous polyposis with an increased risk of CRC and other malignancies. Similar syndromes with predisposition to colonic polyposis include juvenile polyposis syndrome (JPS) and Cowden syndrome. PJS is caused by mutations in *STK11* - gene[52]. Mutations in *SMAD4* and *BMPR1A* genes have been identified in 40%-60% of patients with JPS[53,54]. Mutations in the *PTEN* gene are found in over 80% of patients with Cowden syndrome[55].

One of the most characteristic feature of PJS is the development of multiple hamartomatous polyps of both the small (60%-90%) and large (50%-70%) intestines[56]. Symptoms usually occur in teenage years, however in our series children with polyp-related intussusception and emergency surgery under the age of eight years much higher than anticipated (5% of all PJS patients). Intussusception, gastrointestinal bleeding and bowel obstruction are commonly the first clinical symptoms, apart from the lentiginosis pigmentosa of the lips[57].

Mucocutaneous pigmentation on the lips, periorbital region and buccal mucosa are very consistent in patients with PJS. This mucocutaneous pigmentation in association with hamartomatous polyps are virtually diagnostic for PJS in an individual with a family history of PJS[58,59]. The lifetime risk of cancer development in patients with PJS has been reported to be as high as 85%[60]. Cancers of the GI have been thought to occur in about three quarters of PJS patients including a close to 40% risk for CRC[61].

Since PJS is not associated with complete penetrance with regard to CRC there is no indication for prophylactic surgery. The indications for surgical management are therefore usually symptom related. This is especially true for surgical management of small bowel polyps. The small bowel must be monitored regularly, preferably with video endoscopy and polyps with a size > 1.5 cm should be prophylactically removed, preferably via doubl-balloon endoscopy. Surgical resection of large colonic polyps is indicated following failure of endoscopic polypectomy. Equally, severe dysplasia and malignant transformation constitute absolute indications for surgery. The principles of oncologic resection should be followed when dealing with CRC in a patient with PJS.

PPAP

PPAP is a dominantly inherited condition caused by germline mutations in the DNA polymerases *POLE* and *POLD*[62]. These mutations have been identified in families with a history of unexplained adenomatous polyposis and CRC[63,64]. Extra-colonic manifestations including endometrial, brain and duodenal tumors have been reported in association with PPAP[65]. Typically, a large number of polyps (up to a few hundreds) are present by the age of 35-40 years[66]. Therefore, PPAP should be considered if clinical and endoscopic aspects of FAP, aFAP or MAP are present in the absence of the respective mutations following genetic analysis. Also and interestingly, this syndrome may clinically be consistent with LS, including MSI in the neoplastic tissue.

Estimated risks of PPAP - associated CRC patients with *POLE* mutations by the age of 70 years were reported in a recent publication by Buchanan *et al.*[67] to be 40% for males and 32% for females. The corresponding risks in patients with *POLD* mutations were 63% in males and 52% in females. These estimates must be interpreted with caution due to limited data on this newly described syndrome.

An evidence based management algorithm for PPAP is so far not available. Thus surveillance and surgical management of patients with PPAP should follow the principles of “best clinical practice” analogue to similar syndroms (aFAP and MAP and LS).

NTHL1-ASSOCIATED POLYPOSIS

NTHL1-associated polyposis (NAP) is a recessively inherited polyposis syndrome caused by mutations in base excision repair gene *NTHL1*[68]. Homozygous germline mutations in NTHL1 have been identified in cases with a family history of adenomatous polyposis and CRC[69]. Besides, extra-colonic manifestations might be present[70]. More insight is needed to be able to define the spectrum of presentation and the risk of CRC in patients with NAP. To date, surgical management is symptom related, with no indication for prophylactic surgery at this time.

MSH3 POLYPSIS

Adenomatous polyposis has recently been described in connection with biallelic germline mutations in *MSH3*, an *MMR* gene[71]. The resulting CRC demonstrates microsatellite instability. Although data on this new polyposis syndrome are limited, surveillance and management should follow the principles of “best clinical practice” analogue to LS. Clinically, the phenotype might be indistinguishable from FAP and follow the same (individualized) management recommendations.

DISCUSSION

The management of patients with hereditary predisposition for CRC warrants a good understanding of the underlying syndrome. The syndrome-associated risk for CRC must be considered, especially in the event of a CRC and required surgery. Besides, heterogeneity in mutational status as well as clinical presentation must be considered in each case. Thus an individualized decision-making and a personalized strategy with the patient's active involvement in terms of shared decision-making should represent a major aspect of management.

Basically, the principles of oncologic surgery should be respected in call cases with CRC independent of mutational status. The need for extended surgery beyond segmental colectomy for CRC can be made as a "tailored approach" in selected cases based on mutational status, that is gene and gender. This is a moving target and the challenge lies in the translational aspect of patient management. As an example: LS still may be considered by most as a syndrome with a high risk for colorectal and other GI malignancies. However, depending on the gene, endometrial cancer may be the sentinel cancer and not CRC (*MSH6*). Or, *PMS2* is a very low penetrant gene and mutations may not predispose to a substantial amount of cancers. Therefore annual invasive screening or prophylactic surgery may not be warranted. *MLH1*- and *MSH2*-LS patients, however, have a very high risk for metachronous CRC cancers, despite even yearly colonoscopies. Therefore, patients might opt to have more extended surgery at the time of their primary surgery. Or, especially for *MSH6* mutation carriers, a simultaneous hysterectomy after completion of the family planning might be the preferred option. In order to address these issues it is becoming pivotal to generate genetic tests and a reliable risk assessment as timely as possible following the diagnosis of CRC and prior to cancer surgery.

Prophylactic colorectal resection (restorative proctocolectomy) with or without IPAA is currrently reserved for hereditary syndroms with 100% penetrance for the development of CRC including FAP, aFAP and MAP. The role of prophylactic colorectal surgery for hereditary syndromes without a 100% penetrance is still to be defined and must include patient preference.

Patients with hereditary CRC are usually younger than those with sporadic CRC. Thus quality of life following surgery is of even greater importance to these patients. Therefore attention to technical details with respect to surgery like minimizing surgical trauma and preservation of nerve function during pelvic dissection is a major aspect of surgical management. Furthermore, the postoperative follow-up should be in accordance with syndrome-specific guidelines.

The role of effective chemoprevention for example with aspirin may influence decision-making regarding prophylactic surgery and must be assessed prospectively. In the light of evolving evidence, it is mandatory to involve patients in decision-making with the most recent knowledge available.

In conclusion, with increasing understanding of tumor genetics, the role of gene and gender will increasingly play a role in the management of patients with hereditary predispostion for CRC. A good understanding of the predisposing genetic mutations with regard to mutational and clinical heterogeneity is the basis for an optimized management. Prophylactic surgery is reserved for syndromes with a 100% penetrance. The principles of oncologic resection should be respected as in sporadic CRC. The quality of life following surgical management should be the focus of counselling and decision-making. Postoperative lifelong follow-up is an important aspect of surgical management and must be discussed with patients at the time of their first surgery. The potential role of chemoprevention in individuals with hereditary predisposition to CRC must be prospectively studied and evaluated for less invasive options than prophylactic or prophylactically extended surgeries. Last but not least: after identification of an index patient with a hereditary mutation, genetic counselling and the option of predictive testing must be the focus of the surgeon.

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Authors' contributions

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Mini-invasive Surgery

Review

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The importance of pathological quality control for rectal surgery

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Abstract
Pathologists are an integral member of the colorectal multidisciplinary team and are able to closely interact with surgeons, radiologists and oncologists to facilitate improvements in surgical quality and patient outcomes. Accurate, high quality pathology reports containing all vital prognostic information are essential to ensure the patient receives optimal treatment. These reports should also integrate feedback to all members of the multidisciplinary team on the accuracy of preoperative staging, response to preoperative treatment, and the quality of surgery. Pathologists have played a key role in improving outcomes in patients with rectal cancer by recognising the prognostic importance of an involved circumferential resection margin. In addition, pathologists have described an assessment of the surgical planes of dissection as a marker of surgical quality and thereby a means of quality control. This article will review the current best practice for the pathological assessment of anterior resections and abdominoperineal excisions for rectal cancer and ultimately look at how pathologists can influence quality control in rectal cancer surgery.

Keywords: Rectal cancer, pathological assessment, quality of surgery, mesorectal grading

INTRODUCTION

Pathologists play a key role in the modern multidisciplinary management of patients with rectal cancer. Pathological assessment of the resected specimen not only provides key prognostic information, e.g., primary staging of the tumour and identification of high risk features, but also allows evaluation of the quality of the surgery, accuracy of radiology, and an assessment of response to neoadjuvant therapy. Pathologists therefore have a unique opportunity, and responsibility, to provide feedback to all members of the multidisciplinary team (MDT), in particular surgeons, radiologists and oncologists, on the quality of their services for audit, education and research purposes. This interaction is essential to optimise improving patient outcomes and ensure high quality care for patients with rectal cancer.

Total mesorectal excision (TME) has become the surgical treatment of choice in operable rectal cancer[1], and high quality TME is vital in reducing the risk of local recurrence. If a patient with a low rectal cancer requires an abdominoperineal excision (APE), the mesorectum should be removed intact as for a TME but also careful thought should be given to the plane of dissection around the sphincters/levators. The quality of surgery can be determined by pathological assessment of the plane of dissection compared to the intended planes, with a focus on the mesorectal plane in all major resectional specimens[2] and an additional assessment of the sphincter plane in APE[3]. In addition, involvement of the circumferential resection margin (CRM) can be used as a marker of the quality of surgery, although this is partly influenced by tumour extent[4]. Optimal surgery should aim for an intact specimen in the planned dissection plane with an uninvolved CRM.

Magnetic resonance imaging (MRI) is routinely used to stage rectal tumours preoperatively, to plan the optimal dissection plane and to re-assess tumours following neoadjuvant therapy. Pathologists provide feedback and quality control to radiologists on their accuracy of staging, prediction of CRM involvement, and response to neoadjuvant treatment. Oncologists can also benefit from feedback on response to neoadjuvant treatment, which gives important prognostic information and can be used to tailor further treatment.

Pathologists dissecting and analysing rectal cancer specimens must produce an accurate report not only containing all important staging and prognostic information, but also allowing the evaluation of the quality of other clinical services, notably radiology, surgery and oncology. For this reason, we advocate the use of a structured proforma for reporting, e.g., the Royal College of Pathologists dataset for colorectal cancer[5].

This review will focus on how pathological assessment can be used to evaluate and optimise the quality of rectal cancer treatment as well as the evidence underpinning this.

SURGICAL ANATOMY OF TME/ANTERIOR RESECTION SPECIMENS

Above the anal sphincter complex, the muscularis propria of the rectum is surrounded by a variable layer of perirectal mesenteric fat known as the mesorectum, which is in direct continuity with the mesocolon. The mesorectum is of upmost importance in rectal cancer surgery as it contains all the structures, including blood vessels, nerves, lymphatic drainage, and lymph nodes, by which rectal cancers can potentially disseminate. A layer of visceral fascia completely surrounds the mesorectum below the peritoneal reflections, with this mesorectal fascia continuing posteriorly to the apex of the mesorectal triangle. Above the peritoneal reflections, the anterior and lateral mesorectum is covered by peritoneum [Figure 1]. The mesorectal fascia and peritoneum together create the external surface of a surgical "package", which should be removed intact with optimal TME surgery.

The volume of the mesorectum varies significantly between individuals and in different regions of the structure, with the greatest volume seen posteriorly and a thinner layer anteriorly[6]. It is therefore unsurprising that involvement of the CRM and intra-operative perforations are more commonly seen at the anterior aspect of the specimen[6,7]. The greatest volume of mesorectum is found in the mid rectum, distal to which the structure gradually narrows to a point of maximum wasting at the level of puborectalis, approximately 4 cm above the anal verge[8].

During TME surgery, the aim is to perform precise dissection within the mesorectal fascial plane to create an intact surgical "package" containing the primary tumour and surrounding mesorectum[1]. The non-peritonealised surface of the specimen forms the surgically created CRM, although this margin is only

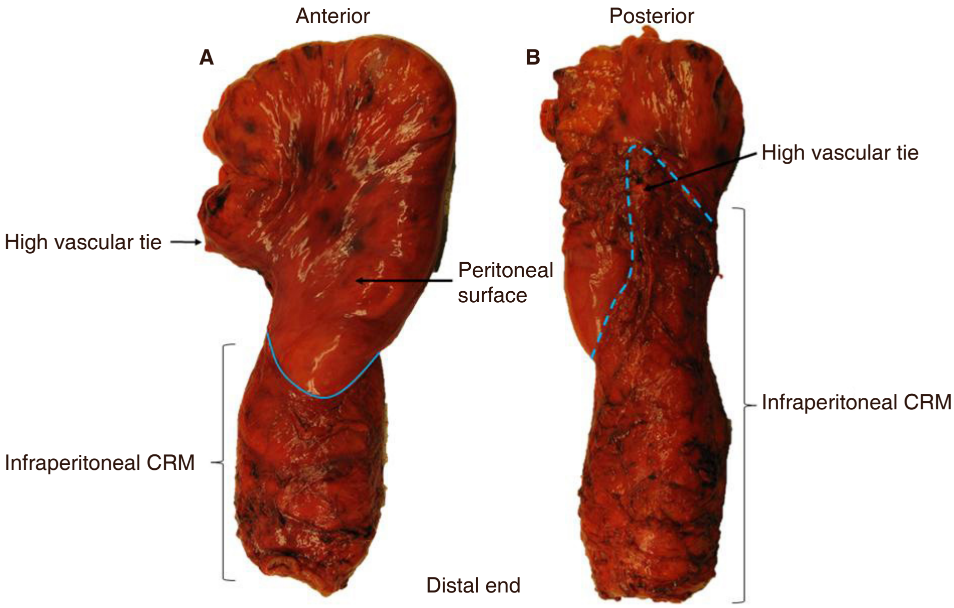

Figure 1. Anterior resection specimen for rectal cancer demonstrating the peritoneal reflection (marked in blue solid line) at the anterior aspect (A) and the mesorectal apex (marked in blue dotted line) at the posterior aspect (B). CRM: circumferential resection margin

truly circumferential below the level of the anterior peritoneal reflection. The CRM should be covered by mesorectal fascia if surgery has been carried out in the optimal mesorectal plane[1].

Involvement of the CRM by tumour, defined as tumour 1 mm or less from the margin, is strongly associated with local recurrence and is an adverse prognostic feature[4,9]. This involvement can occur through direct extension of the main tumour; by tumour in nerves, blood vessels, lymphatic channels or lymph nodes; or discontinuous tumour deposits[5]. Advances in MRI mean that radiologists can make excellent predictions for CRM involvement and play a vital role in selecting patients who may benefit from preoperative therapy[10].

There are two main causes of the primary tumour involving the CRM. Either the tumour is advanced and involving the mesorectal fascia, or the tumour is clear of the fascia but the surgeon has failed to stay in the correct dissection plane. Advanced tumours extending to within 1 mm of the mesorectal fascia should be identified in advance by MRI and may benefit from more extensive surgery or preoperative treatment to shrink the tumour to a surgically resectable state. If the CRM is involved by primary tumour with the specimen in the mesorectal plane, either the involved CRM should have been expected or the radiologist has failed to identify the advanced nature of the disease.

The introduction of TME and surgical training initiatives have led to a significant reduction in the rate of local recurrence and improved survival in both large-scale population series and clinical trials[11-13]. A major contributing factor to this improvement is thought to be the reduction in CRM involvement and suboptimal planes of surgery associated with TME[4].

SURGICAL ANATOMY OF APE SPECIMENS

APE of the rectum and anus is frequently utilised as the surgical treatment of choice in patients with advanced low rectal tumours (within 6 cm of the anal verge), although the operation may be used for higher tumours if poor function is predicted. The “conventional” APE involves an abdominal and a perineal phase; the abdominal phase is essentially a TME, and this is followed by the perineal phase, traditionally with the patient in the lithotomy position, that involves dissection outside the anal sphincters to meet the TME plane.

Approximately 25% of patients with rectal cancer undergo APE surgery, although there is considerable variation in APE rates between hospitals[14,15]. There have been concerns raised that APE surgery is overused in some centres and it has been proposed that the rate of APE surgery may be used as a surrogate marker for surgical quality[16,17]. The outcome after APE surgery for low rectal cancer in several studies is poorer in terms of patient outcome when compared to anterior resections for higher rectal tumours[6,18]. As previously described, the mesorectum narrows to a waist at the level of puborectalis and commencement of the sphincters, therefore unlike mid or high rectal tumours, there is less protective tissue between the tumour and the CRM in low rectal tumours when following the "conventional" TME plane. In addition, visualisation in a "conventional" APE may be poor in the lithotomy position during perineal dissection and may lead to surgeons deviating into the wrong tissue plane. These factors are likely to account for the increased CRM involvement rate in APE surgery[6,7] and increased risk of intraoperative perforations[19,20]. In cases of advanced anterior tumours, an en bloc prostatectomy or resection of the posterior vaginal wall may be carried out due to the negligible perirectal tissue present anteriorly, in order to increase the chances of an R0 resection[6].

Development of more radical techniques for advanced tumours, e.g., extralevator APE has led to improved clinical outcomes in some studies through a reduction in CRM involvement and perforations compared to "conventional" APE surgery[7,21,22]. Extralevator APE involves the removal of the levator ani with the mesorectum and anal sphincters, creating a more cylindrically shaped specimen and thereby providing critical extra tissue around a low rectal tumour[22]. Surgical variations in this technique, including use of the prone jack-knife position, mean that visualisation of the perineal dissection is also improved, helping to reduce the risk of straying into the wrong tissue plane[22]. A multicentre European study comparing a large series of extralevator APE to "conventional" APE found that extralevator APE removed significantly more tissue around low rectal cancers with a reduction in CRM involvement (50% to 20%, $P < 0.001$) and reduction in intraoperative perforations (28% to 8%, $P < 0.001$)[23]. Similarly, a 2011 systematic review found a reduction when comparing extralevator APE to conventional APE in CRM involvement (9.6% *vs.* 15.4%, $P = 0.022$), bowel perforation (4.1% *vs.* 10.4%, $P = 0.004$), and local recurrence rate (6.6% *vs.* 11.9%, $P < 0.001$)[24].

THE ROLE OF PHOTOGRAPHY IN SPECIMEN QUALITY CONTROL

A key component in facilitating feedback on the quality of surgical specimens is keeping a permanent record of each specimen using digital photography. Digital images should be taken of the anterior and posterior aspect of the whole intact specimen, preferably prior to inking, opening and fixation, alongside a metric scale for calibration. Any significant defects in the mesorectal fascia, sphincters or perforations warrant a close-up image. Similarly, digital images should be routinely taken of the serial cross-sectional slices taken at 3-5 mm intervals through the tumour to confirm the plane of surgery and demonstrate the relationship of the tumour to the CRM. In APE, additional close-up images should be taken of the front and back of the anal canal/sphincter/levator area to record the plane of surgery in this area. Lateral images may also be helpful. These images should be stored in a departmental archive and should be actively used in MDT meetings to feed back to surgical colleagues and compare to the radiological appearances. In addition they can be used for education, research and audit purposes.

PATHOLOGICAL ASSESSMENT OF ANTERIOR RESECTION SPECIMENS

The anatomy of the specimen depends on several factors including the positioning of the tumour, the quality of surgical dissection, whether a partial or total mesorectal excision has been performed, whether additional structures have been removed and the individual variation in height of the peritoneal reflections. The first step is to grade the quality of the mesorectum. The recommended three-point grading system for assessment of mesorectal dissection can be seen in Table 1[25] and macroscopic images demonstrating these planes of dissection can be found in the Royal College of Pathologists dataset for colorectal cancer[5]. Examples of mesorectal and intramesorectal plane surgery can be seen in Figure 2.

Table 1. Three-point grading system for the assessment of the plane of mesorectal dissection in total mesorectal excision/anterior resection specimens for rectal cancer

Grade of excision	Quality of surgery	Description
Mesorectal	Good surgery	Intact smooth mesorectal surface with only minor irregularities. Any defects must be no deeper than 5 mm. No coning of the specimen distally. Smooth CRM on slicing
Intramesorectal	Moderate surgery	Moderate bulk to mesorectum but irregularity of the mesorectal surface. Moderate distal coning. Muscularis propria not visible with the exception of levator insertion. Moderate irregularity of CRM on slicing
Muscularis propria	Poor surgery	Little bulk to mesorectum with defects down onto the muscularis propria and/or very irregular CRM. It includes perforations through the CRM

CRM: circumferential resection margin

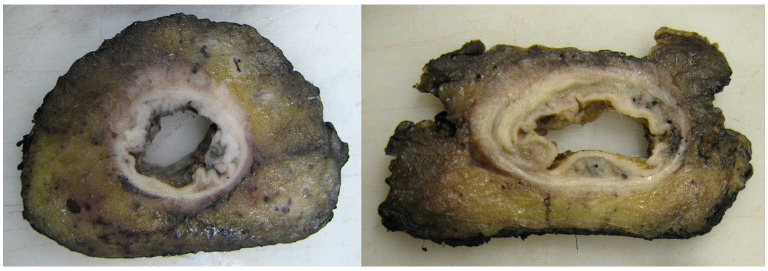

Figure 2. Cross sectional slices showing a mesorectal plane specimen with smooth circumferential resection margin (CRM) (left) and intramesorectal plane specimen with irregularity to the CRM and obvious defects, but no evidence of defects extending to the muscle tube (right)

Grading of the mesorectal plane of excision is a key marker for surgical quality and plays a vital role in providing continual feedback to the MDT team for educational and audit purposes. Feeding back the planes of mesorectal surgery in the MRC CR07 trial led to a gradual improvement in specimen quality over the duration of the trial[26].

Prior to dissecting the specimen, the external surface should be carefully examined by a histopathologist to ensure all key prognostic features are identified and described. We recommend the description and dissection method developed in Leeds and adopted by the Royal College of Pathologists for use in colorectal cancer reporting to ensure consistent and thorough assessment[5,27]. It is essential that the specimen is received intact, and preferably fresh, to allow accurate assessment of both the mesorectal plane and the CRM, as well as taking the whole specimen photographs. The mesorectal fascia may be easier to identify and assess in fresh tissue as it will appear as a shiny smooth layer, whereas following formalin fixation the fascia can become distorted and appear dull and opaque.

Any disruptions in the mesorectal fascia should be described in terms of their depth and extent, and the presence of surgical perforation, a communication between the surface of the specimen and the lumen of the bowel, should also be documented in the pathology report [Figure 3]. Tumour perforations above the peritoneal reflections are associated with an increased risk of intraperitoneal recurrence and have a poor prognosis[28]; these are classified as pT4a using TNM8 staging[29]. Perforations through the CRM commonly occur in addition to perforations through the peritoneum, especially in APE specimens, and usually involve the anterior aspect, where the mesorectum is at its thinnest[19]. Although technically not classified as pT4a under TNM rules, these are also associated with a high risk of local recurrence[20] and reduced survival[30].

PATHOLOGICAL ASSESSMENT OF APE SPECIMENS

APE specimens should be received intact, ideally fresh and should be assessed by pathologists in a very similar way to that for anterior resection specimens as described above. Specifically, the mesorectal plane of excision and presence of intraoperative perforations should be evaluated and specimen photographs should

Figure 3. Anterior resection specimen showing a large anterior perforation with a defect into the lumen of the bowel (left), which is confirmed on cross sectional slicing where part of the anterior rectal wall is missing (right)

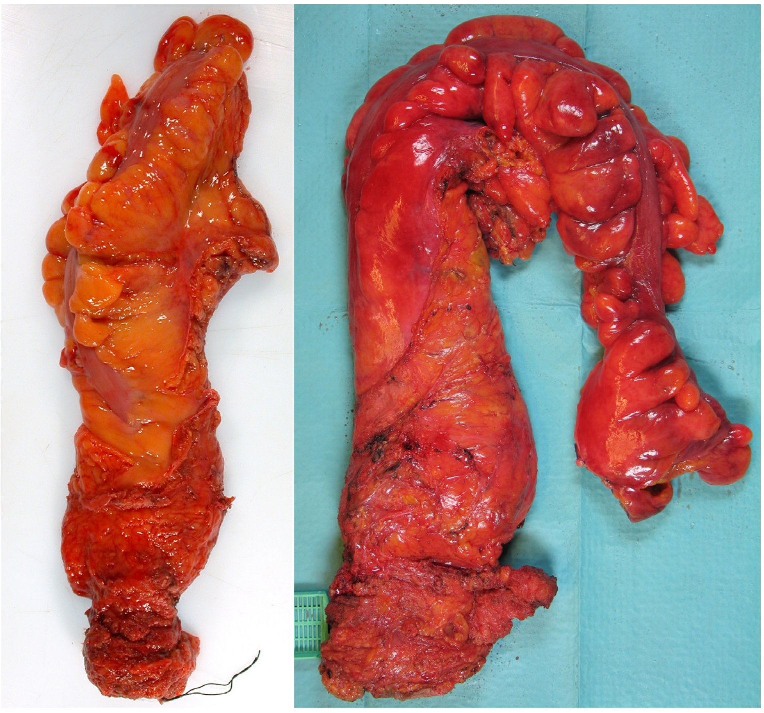

Figure 4. Two abdominoperineal specimens, the first resected in the sphincteric plane with an obvious area of waisting towards the base of the mesorectum/top of the sphincters (left) and the second resected in the extra-levator plane with no visible waisting (right)

be taken. An additional assessment of the surgical plane of dissection around the levator/sphincter area is an important indicator of APE quality and needs to be assessed carefully by the pathologist; macroscopic images demonstrating the three surgical planes of dissection can be found in the Royal College of Pathologists dataset for colorectal cancer[5]. A study by Martijnse *et al*.[31] is an example of how an increased focus on the quality of perineal dissection in APE surgery can lead to improved quality of surgery and a significant reduction in the number of involved resection margins [Figure 4]. The recommended three-point grading system can be seen in Table 2[3].

PATHOLOGICAL ASSESSMENT OF THE CRM

Involvement of the CRM is a key prognostic marker in rectal cancer and therefore care needs to be taken to ensure accurate histopathological assessment. The importance of an involved CRM increases after preoperative treatment as it is associated with increased risk of local failure, local recurrence and poor survival[9,18].

Following macroscopic assessment of the mesorectal plane (and sphincter planes in APE), whole specimen photography and after a period of formalin fixation (at least 48 hours to facilitate thin cross sectional

Table 2. Three-point grading system for the assessment of the plane of anal canal/sphincter dissection in abdominoperineal excision specimens for low-rectal cancer

Grade	Description
Extra-levator plane	The specimen has a cylindrical shape due to the presence of levator ani removed *en bloc* with the mesorectum and sphincters. Any defects must be no deeper than 5 mm. No waisting of the specimen. Smooth CRM on slicing
Sphincteric plane	The specimen is waisted and the CRM in this region is formed by the surface of the sphincter muscles which have been removed intact
Intrasphincteric plane	The specimen is waisted and includes deviations into the sphincter muscles, submucosa and complete perforations

CRM: circumferential resection margin

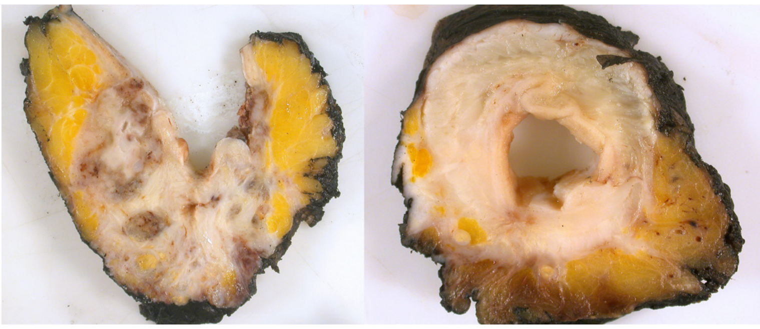

Figure 5. Cross sectional slices from two specimens showing involvement of the circumferential resection margin (CRM) by primary tumour. The first has macroscopically visible tumour extending to the margin and was correctly identified as CRM involved on MRI (left); the second has extensive fibrosis following pre-operative chemoradiotherapy and the post treatment MRI predicted a clear margin, but small microscopic islands of residual viable tumour were present at the CRM (right)

slices), the CRM of the specimen should be inked, e.g., with India ink to allow histological identification of the margin and accurate measurement. It is important that the peritoneal surface is not inked as involvement of the peritoneum is a risk factor for peritoneal recurrence rather than the local recurrence seen following CRM involvement.

The specimen should then be sliced transversely at 3-5 mm intervals and the slices laid out sequentially to visualise the relationship between the tumour and the CRM. A minimum of five tumour blocks should be processed for histological examination and at least one should include the closest tumour to the inked CRM[5]. Tumour can involve the CRM through primary extension, discontinuous spread/tumour deposits, lymph node metastases (with and without extracapsular spread) and along nerves, veins and lymphatics [Figure 5]. Any lymph nodes or suspicious vascular structures close to the CRM should therefore be embedded with the inked margin intact. It is mandatory that the pathology report includes a comment regarding tumour involvement of the CRM, as if appropriate the patient may be offered adjuvant therapy to reduce the subsequent risk of local recurrence[5,32]. The nearest distance of the tumour to the CRM should also be recorded and if involved the mechanism and extent of involvement may be helpful. It should be noted that the relative importance of lymph node metastases at the CRM is relatively underreported, however, limited evidence suggests that this may have less impact than other mechanisms of involvement[4]. Biologically one would expect that tumour in a lymph node with an intact lymph node capsule and intact mesorectal fascia is likely to have a lower risk of local recurrence when compared to extracapsular lymph node spread with mesorectal defects.

The status of the CRM and mechanisms of involvement should be specifically fed back to the radiologists at the MDT meeting to enable them to audit their preoperative predictions for CRM involvement. Radiological assessment following neoadjuvant therapy is of increasing importance; MRI prediction of involvement of the CRM following preoperative treatment is associated with a greater risk of local recurrence[33]. Feedback from the pathologist as to whether any fibrosis extends towards the CRM is very helpful to enable correlation with MRI findings. In cases where there is a discrepancy between the radiological prediction and the final pathology, effort should be made by the pathologist to indicate why this is the case. One important factor may be correlation with the plane of surgery, i.e., an involved margin being caused by failure to resect in the planned dissection plane. Another common cause of discrepancy is the identification of CRM involvement through microscopic nodal deposits and small vessel invasion that could not be visualised radiologically.

Feedback on the degree of response to neoadjuvant treatment is also very helpful for the oncologists in terms of regression away from the CRM and general tumour regression grading in order to understand the sensitivity of individual tumours to specific treatments and to plan subsequent treatment. The four point tumour regression grading system from TNM8 should be used in all pathology reports; this can be found in the latest Royal College of Pathologists dataset for colorectal cancer[5,29].

THE ROLE OF MDT EDUCATION IN IMPROVING THE QUALITY OF TREATMENT FOR RECTAL CANCER

The MDT provides a patient-centred forum and an opportunity to optimise the treatment plan, improve quality of care for patients with cancer, and is likely linked to improved rates of curative resection[34]. Education of the MDT gives a unique opportunity to optimise surgical practice, improve decision making for preoperative treatment, and advance the overall quality of care for patients[35]. Education programmes directed primarily at surgeons have been shown to improve the oncological quality of surgical specimens and patient outcomes in Netherlands, Norway and Sweden[13]. The National Pelican MDT TME Development Programme was an educational programme aimed at the whole CRC MDT and was delivered through the Pelican Cancer Foundation in England[36]. Although there is limited evidence for the direct effect of the programme, outcomes for rectal cancer patients in the UK were significantly improved over this time period and a further government funded National MDT educational programme focusing on low rectal cancer called the Low Rectal Cancer Development Programme (LOREC) was launched a few years later[37]. The aim of LOREC was to improve the poor outcomes associated with low rectal cancer by focusing on preoperative imaging, selective neoadjuvant therapy, optimal surgical treatment, specialist nursing, and detailed histopathological assessment. LOREC ran workshops for all colorectal MDT members and take-up across England was excellent with approximately 90% of MDTs attending and a total 1019 participants[3 7]. These received excellent feedback and 96% of surgeons attending said it would alter their future practice[37,38]; local audit has also shown a change in surgical practice associated with good outcomes following the workshops[39]. LOREC has shown the potential positive impact that education on MDTs can have. A further programme focusing on early colorectal cancers, the Significant Polyp & Early Colorectal Cancer, has recently finished and there is an ongoing programme, Improving Management for Patients with Advanced Colorectal Tumour, with a focus on advanced and metastatic cancers[40].

CONCLUSION

Outcomes for patients with rectal cancer have markedly improved over the last two decades; these improvements have resulted from a number of interventions including the description and widespread introduction of TME surgery[1,41], the use of MRI for preoperative staging[42,43], and the use of neoadjuvant treatment[44,45]. Histopathologists who dissect and report rectal cancer specimens have played an essential role in improving patient outcomes by recognising the importance of the CRM[9], as well as describing the assessment of surgical planes of dissection as a means of quality control[26]. More recent focus has been on the poor outcomes associated with traditional APE surgery for low rectal cancer and pathologists have played a vital role in this, by identifying evidence to support changes in practice for surgeons, radiologists, oncologists and pathologists. Many of these improvements have been supported by national MDT education/development programmes leading to a rapid uptake in optimal practice.

In summary, pathologists are able to assess the quality of surgery of anterior resections by assessing the plane of mesorectal excision, involvement of the CRM and presence of intraoperative perforations. In APE specimens, the same quality markers are used with the addition of an assessment of the plane of sphincter/levator dissection as a surrogate marker for surgical quality in the critical area commonly associated with CRM involvement/perforations. Feedback on the planes of surgery, as well as other important prognostic information, is essential to the MDT and can benefit not only surgeons, but oncologists and radiologists. Pathologists must provide detailed, accurate reports encompassing all important prognostic markers as well as an evaluation of surgical quality. Consistent feedback to the colorectal MDT is essential to further improve outcomes for patients with rectal cancer.

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Author's contributions

Equally involved with the literature research and manuscript writing: Westwood AC, West NP

Availability of data and materials

Not applicable.

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Conflicts of interest

The two 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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Mini-invasive Surgery

Opinion

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Aspirin and colorectal cancer chemoprevention

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Abstract
The role of aspirin in colorectal cancer prevention is currently under intense scrutiny. Low dose Aspirin effectively suppresses the cyclooxygenase-2 enzyme system, which is thought to play an important role in the pathogenesis of colorectal cancer. A number of observational studies and randomized controlled trials have supported a chemoprevention effect. In some instances, regular use of low dose aspirin has provided a nearly 20% reduction in incidence. Compliance and underutilization remain important issues however, as does the incidence of side effects - aspirin is a non-steroidal anti-inflammatory drug, and regular use of these medications carries a small but significant risk of gastrointestinal bleeding, which on occasion, can be life-threatening. These are important problems, which need wider recognition and detailed exploration before we can suggest widespread use of aspirin in primary or secondary prevention.

Keywords: Colorectal cancer, adenomas, aspirin, non-steroidal anti-inflammatory drugs, chemoprevention, cyclooxygenase-2

INTRODUCTION
The incidence of rectal cancer has increased over the last decade[1]. Left undiagnosed, patients can present with untreatable or stage IV disease, and even when recognised relatively early, cases are often locally advanced, and require a combination of major surgery, chemotherapy and radiotherapy to attempt cure.

With the advent of laparoscopic, and now robotic resection, the rectal cancer patient is relieved of some of the discomforts of treatment, but one of the most desired intentions of rectal cancer treatment would be to prevent or treat the disease at an earlier stage. Most left-sided cancers develop from an earlier adenoma

Table 1. Observational studies with aspirin and colorectal cancer chemoprevention

Study	Design	Aspirin use	Duration	Relative risk
Nurses Health Study[8]	Cohort	More than 2x per week	10	0.62
Cancer Prevention Study[9]	Cohort	Various	15	0.58-0.61
Health Professionals Study[10]	Cohort	More than 2x per week	4	0.54

phase. We now know that unregulated prostaglandin expression appears to have some importance in the early phase of adenoma formation, and transition to invasive cancer[2,3].

COLORECTAL CANCER CHEMOPREVENTION

The cyclooxygenase (COX) enzymes act on arachidonic acid to permit formation of prostaglandins. There are two isoenzymes; Generally speaking, although this is slightly simplistic, COX-1 is responsible for stable expression of "useful" prostaglandins in cells[3,4], whilst COX-2 expression occurs by stimulation in various pathological environments, and typically by those factors which are present in malignant disease and chronic inflammation[5,6]. Once induced, COX-2 can create a situation of uncontrolled prostaglandin release, which thereby promotes the genesis and growth of malignant cells in various ways[7]. A cell which is initially only mildly dysplastic, can, in the environment of persistent prostaglandin release, transform into more severe dysplasia and frankly, cancer.

The adenoma-cancer transformation occurs over many years in most patients, although there are exceptions. The lag period provides a potential pathway for a suitable intervention to reduce cancer risk - typically, we have thought about polyp removal in this regard, the purpose of colon cancer screening program, now prevalent in most countries. What if however, we could terminate the transition of the cell on the brink of turning dysplastic or malignant in some way, with drugs that inhibit prostaglandin synthesis?

Low dose aspirin, already taken worldwide to in the secondary prevention of ischaemic heart disease, blocks COX and prostaglandin formation, so would seem to be a prime candidate. Indeed, studies as far back as 20 years ago suggested some usefulness in this regard[8-10][Table 1]. The results of formal randomised controlled trials (RCTs) in the 1990s and early 2000s were disappointing however, and did not substantiate results from previous observational studies[11,12].

Towards the end of the last decade however, the longer term results of the aforementioned RCTs and other more recent trials suggested a significant reduction in colorectal cancer incidence after 10 years of use[13,14] [Table 2].

Patients probably need to take aspirin or related drugs regularly for about 3 years before realising an anti-cancer benefit, and even if they then stop using the medication, there still may exist some long term protective effect lasting up to 10 years or more, which indicates we might be able to suggest patients take aspirin for a defined period, and then be less strict about compliance and adherence after that time, particularly if there is an issue with adverse effects.

Furthermore, another positive insight from trials is that maintaining patients on a low dose for example, 75-81 mg, is sufficient to allow risk reduction in those with a polyp history[15,16] - this was actually previously also suggested by observational work[17].

An anticancer action for aspirin at low dose seems paradoxical however - extraordinarily high doses of aspirin (over 1 g/day) are required to terminate COX-2 expression in nucleated cells[18]. Recent studies suggest the low dose strategy works due to inactivation of platelet COX-1 - a strong induction signal for COX-2 upregulation in damaged cells[19]. Recent work also indicates there may be other isolated mechanisms

Table 2. Long term follow-up data from randomised controlled trials

Study	Design	Duration (years)	Number of patients	Colon cancer hazard ratio	*P* value	GI bleed/ peptic ulcer
Cook NR[13]	Post RCT observational follow-up	10	33,682 (84.5% of original participants)	0.80 overall (0.73 proximal tumors)	0.021 (0.022)	
Rothwell PM[14]	Post RCT data follow up (5 trials)	20	17,164	0.58 rectal (0.35 proximal tumors)	< 0.01	Not reported

of effect to prevent cancer - the phosphatidylinositol 3-kinase-related pathway[20], "induced-senescence" by interference of the sirtuin1 metabolic pathway[21], and clotting factor acetylation[22].

The aforementioned provides strong support for the case for using aspirin to prevent rectal cancer, but there are serious potential problems that need consideration.

Firstly, there is the small but dose-dependent risk of haemorrhagic stroke and gastrointestinal bleeding[23]. This might be deemed relatively acceptable in patients already on aspirin for ischaemic heart disease, but could be a serious issue in younger and otherwise healthy patients being asked to take the medication for chemoprevention long term - and has been noted as a risk in randomised controlled trials [Table 2].

Secondly, there are known to be cases where aspirin does not "work", even when taken regularly. This phenomenon of persistent platelet activation has long been recognised as a cause of persistent strokes/angina or myocardial infarction in around one quarter of compliant patients taking therapeutic dose aspirin[24,25].

The reasons for "aspirin resistance" are variable, probably involving supranormal rates of platelet turnover in some patients, suboptimal levels of actual agent entering the circulation, and possibly different pathways for thromboxane A2 synthesis and abnormal variants of COX[26]. Aspirin bioavailability can vary from 20%-40% and differs markedly depending on route of administration, and formulation - for example, soluble aspirin has better bioavailability than tablet form[27,28], and some co-administered agents and lifestyle factors can have profound effects on bioavailability[29,30].

Tolerance occurs over time, and is not completely responsive to increased dosing[31]. Studies of aspirin use in cardiovascular disease indicate compliance and non-adherence are significant problems - associated with age, co-morbidity and polypharmacy - essentially in groups who would probably benefit from aspirin most[32]. Our own preliminary work suggests that although side effect reporting is low (< 6%), only a quarter of patients are fully compliant with treatment[33], and underuse may be associated with female gender, the presence of comorbidities and polypharmacy.

CONCLUSION

In summary, regular low dose aspirin would seem to be an ideal candidate for low risk prevention of rectal cancer based on the most recent research, however, concerns about side effects, underutilisation and compliance may indicate a selective role only. In the prevention of ischaemic heart disease, aspirin use is restricted to specific subgroups, and not recommended for general use in primary prevention due to the incidence of the aforementioned side effects in otherwise healthy patients. One potential target group could be those at higher risk of a heart attack or stroke, and who do not have risk factors for stomach bleeding, with the aim of preventing both cardiovascular disease and colorectal cancer. Concerns regarding adverse effects might also limit use of aspirin in those groups at particular risk of colorectal cancer, such as patients with hereditary polyposis or Lynch syndrome, and more work is required to clarify the risk - benefit ratio in these high risk groups.

DECLARATIONS

Authors' contributions

Singh-Ranger G conceived and wrote the article.

Availability of data and materials

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Conflicts of interest

There are no conflict of interests.

Ethical approval and consent to participate

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Consent for publication

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Mini-invasive Surgery

Review

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Transanal minimal invasive surgery - pushing the boundaries of transanal surgery

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Abstract

Transanal minimally invasive surgery is a rapidly evolving platform surgery that is facilitating the transanal approach to colorectal surgery. Over the years since its initial description, the applications have widened and now include endoluminal and extraluminal approaches to rectal and pelvic surgery. This article discusses the various applications and future direction of research evaluating this novel technique and its role in colorectal practice.

Keywords: Transanal minimal invasive surgery, rectal surgery

INTRODUCTION

Transanal minimally invasive surgery (TAMIS) describes a platform that evolved from transanal techniques to address mid to low rectal lesions. It represents an alternative to conventional transanal excision of rectal lesions, transanal endoscopic microsurgery (TEM)/transanal endoscopic operation (TEO) and endoscopic submucosal dissection in selected rectal lesions. TAMIS was introduced in 2009 by Atallah *et al.*[1] for the purpose of performing endoluminal rectal surgery, and its use has since expanded to include extraluminal approaches, most prominent of which is the transanal total mesorectal excision (taTME) for rectal cancers. Instead of a purpose-designed proctoscope as is the case with TEM, TAMIS is characterised by the use of a single-site port transanally in combination with ordinary laparoscopic instruments, a laparoscopic camera lens, and a standard laparoscopic carbon dioxide insufflator. It was developed out of the need for a practical alternative to TEM that was both affordable and technically feasible without specialized equipment[2]. The benefit over TEM was mostly in overcoming the steep learning curve and associated expense. Other reported benefits favouring TAMIS include rapid set-up time, 360 degrees *vs.* 220 degrees of visibility within the rectal lumen, the adaptability to available laparoscopic instruments, and the ease of patient and equipment positioning within the operating theatre[2-4]. Furthermore, it is hypothesised that the soft transanal access platform with TAMIS offers less sphincter traction, although this has not been conclusively demonstrated to translate to better functional outcome postoperatively[4].

The evolution of TAMIS has seen a rapid progression into a technique that is now an established practice of some colorectal surgeons globally and has seen some of the cutting-edge developments in surgical innovation in colorectal surgery[5,6]. Since the inception of TAMIS, several changes have been made to optimize the technique and broaden indications, reflecting the stages described by the IDEAL ("Idea, Development, Exploration, Assessment, Long-term study") framework for surgical innovation[7-9]. The ease of access to the rectum and pelvis that is provided by TAMIS allows it to be used for various additional applications. In this article, we discuss the widening applications and latest developments in TAMIS use, which signpost the future direction with this new platform.

EARLY APPLICATION

Local excision of rectal neoplasia

Initially TAMIS was used largely for local excision of rectal lesions within the context of benign (e.g., adenomatous polyps unsuitable for endoscopic resection) or early-stage (T1) malignant tumours with a low risk for lymphatic involvement at the time of operation or local excision as a form of palliation in patients (T3 and above) who are medically unfit or unwilling to go ahead with standard oncologic surgery[10-13]. Studies report similar advantages conferred with TAMIS as for TEM when compared with conventional transanal resection, with more intact, non-fragmented specimens, negative resection margins and lower recurrence rates[6,12]. For very distal lesions or those at or just above the dentate line, a hybrid approach with standard transanal and TAMIS equipment can facilitate resection[12,14]. TAMIS has also been considered in local excision of tumour site in patients with locally advanced rectal cancer following neoadjuvant therapy; for the purpose of confirming mural complete pathologic response[15]. This approach is considered acceptable in certain scenarios in view of the low risk of occult node positivity for ypT0 lesions is low, at 3%-6%[12,16-19]. There is limited data evaluating the effectiveness of TAMIS for resection of neuroendocrine (e.g., carcinoid tumours) however, small series suggest it is feasible for excision of small primary rectal carcinoids, or following incomplete endoscopic removal[15,20]. A systematic review in 2014[10] reported on a combined 390 TAMIS procedures for local excision of rectal neoplasia with publications from 16 countries. They reported an average excised lesion size of 3.1 cm (range 0.8-4.75 cm) with an average distance of 7.6 cm from the anal verge (range 3-15 cm). Of the 390 TAMIS procedures included, 152 lesions were benign (adenomas and high-grade dysplasias) 209 were malignant (carcinomas in situ/adenocarcinomas), 23 (0.05%) were for neuroendocrine lesions (e.g., carcinoid), three were for fibrosis (e.g., benign scar), one mucocele, one gastrointestinal stromal tumour, and one melanoma[10]. Within the series there were 29/390 complications (7.4%), the most common of which was self-limiting bleeding (10/29). Only five cases (1.28%) were graded on the Clavien Dindo classification as grade 3 (one case of bleeding requiring reintervention and four cases of inadvertent peritoneal entry) and no complications were graded higher. The conversion rate was 2.31% (n = 9) necessitating either a transanal excision with a Park's retractor, TEM surgery or laparoscopy. The recurrence rate was low at 2.7% (7/259), albeit with only short term follow-up, with mean duration of follow-up of approximately seven months. The concept of local excision for rectal cancer is of course a hotly debated topic with both strong proponents and opponents. The role of radiotherapy followed by local excision for early rectal cancers is an emerging field and has the potential for a complete re-evaluation of current standards in rectal cancer surgery with a larger emphasis on organ preservation. A phase-II study enrolled 63 patients with T3 or low-lying T2 rectal cancer who received local excision after achieving complete response to neoadjuvant chemoradiation[21]. They found excellent cumulative 3-year overall survival (91.5%), disease-free survival (91%) and local disease-free survival (97%) in the 43 patients who fulfilled the criteria for watchful surveillance after local excision[21]. A different study compared the functional outcomes and quality of life of local excision *vs.* total mesorectal excision after chemoradiation, and found that local excision achieved better results in both[22]. The paucity of data will probably benefit from prospective studies which have been set to assess the role of organ preserving strategies in a selected category of rectal cancer patients, and TAMIS would probably be the ideal surgical approach[23,24]. One other innovative indication for the TAMIS platform is the recently described transanal endoscopic submucosal resection which is a hybrid procedure combining the skills of the endoscopist and the laparoscopic surgeon to remove large and complex rectal lesions (up to 18 cm in length). Preliminary results on 17 patients from a tertiary referral centre, with complex lesions (> 5 cm lesions, recurrent polyps with submucosal fibrosis) demonstrated the feasibility of the technique[25]. Pioneers of the procedure reported 91% complete endoscopic excision in a single session, sometimes requiring the combination of more than one endoscopic technique (27% of cases)[26]. Intraoperative bleeding (72.7%) was successfully controlled with clips and coagulation; suturing was performed in 9%. Of those who completed the 3-6 months follow-up none developed recurrences, whereas one patient was referred to surgery for a malignant polyp. Such innovations push the boundaries of minimally invasive surgery as previously patients with large/complex lesions would have required an anterior resection.

WIDER APPLICATIONS OF THE TAMIS PLATFORM AND FUTURE DIRECTION

The TAMIS platform has seen rapid evolution, and the breath of applications continues to increase[12]. Some of these will be discussed below.

Transanal total mesorectal excision approach to rectal cancer excision

The spectrum of pathology that can be managed with TAMIS has broadened from excision of intraluminal small rectal lesions to a full total mesorectal excision (TME)[14,27]. In 2015, Lacy *et al.*[28] reported on their experience in 140 cases, using a hybrid approach of transabdominal-taTME and several other series have followed. The TaTME International registry is a prospective, secure online database where surgeons can upload data of TAMIS proctectomy performed on a voluntary basis (https://tatme.medicaldata.eu/). TaTME has been associated with poor pathological outcomes in less than 7.5% of patients, who - of note - received surgery during the first years of technique development[29]. The latest analysis available of patients from the registry included data on 1540 rectal cancers, and confirmed the feasibility and safety of this technique highlighting the key points for optimal short-term outcomes[30]. The keenly anticipated COLOR III trial[31] aims to compare laparoscopic with taTME and should help address questions on the quality of surgery in particular the oncological outcomes in the treatment of mid-low rectal cancers.

TAMIS for benign rectum excision

In 2012, Wolthuis *et al.*[32] described a case report of transanal single port access to facilitate distal rectal mobilization with hand-sewn coloanal anastomosis for a patient with refractory pelvic inflammation secondary to cryptoglandular fistula. In so doing, they proposed the further development of hybrid procedures in paving the way to full transanal resection. TAMIS has since been used in hybrid technique with transabdominal laparoscopic surgery/single incision laparoscopic surgery (SILS) for rectal excision in the context of inflammatory bowel disease. This includes proctectomy in Crohn's disease and also for restorative proctocolectomy (RPC) or completion proctectomy and ileal pouch-anal anastomosis [i.e., transanal ileal pouch anal anastomosis (IPAA) or ta-IPAA] in ulcerative colitis (UC)[33-36]. Ta-IPAA is done either as a 2-stage (total proctocolectomy and IPAA/closure of ileostomy) or 3-stage procedure, i.e., with (subtotal colectomy/proctectomy and IPAA/closure of ileostomy)[34]. Ta-IPAA is often performed with close rectal dissection and single stapled anastomosis. Early reports suggest the TAMIS platform is a feasible and safe alternative to conventional laparoscopic RPC performed for UC. Advantages suggested include the facilitated pelvic dissection, avoidance of repeated application of staplers and when combined with SILS approach results in fewer scars with improved cosmetic results[34]. In 2017, a retrospective comparative study assessing ta-IPAA (n = 97 patients) *vs.* transabdominal minimally invasive (completion) proctectomy with IPAA (119 patients) assessed 90-day morbidity between the two groups[37]. They demonstrated safety of the ta-IPAA approach in patients with UC, with decreasing rates of postoperative morbidity, lower conversion rate and shorter postoperative length of stay[37]. An analysis of the benign cases extracted from the TaTME International registry reported leak rates of less than 5% in the first 69 Ta-IPAA patients included, with 23% overall complication rates (most of them grade I-II Clavien-Dindo)[38]. Similarly, analyses of the entire cohort of patients with inflammatory bowel disease who underwent TAMIS proctectomy with or without restoration of the continuity confirmed the safety of the technique[39]. Four percent experienced Clavien-Dindo III complications; surgery was, however, technically more demanding in Crohn's disease with inability to proceed with TAMIS in 20% of patients and more frequent wound complications[39].

The techniques employed offer an added advantage as a form of natural orifice transanal endoscopic surgery with laparoscopic/SILS assistance and is potentially a well suited technique for inflammatory bowel disease[33,36,40,41]. Recent European guidelines on surgery in UC[42] acknowledge these new variants of natural orifice surgery (i.e., TAMIS for proctectomy with or without an anastomosis). However, in view of their an early development stage, it is noted that future prospective (and comparative) studies would be required to assess benefit in terms of functional outcomes and their role in management of patients with UC[42].

Redo pelvic surgery

In 2016 Borstlap *et al.*[43] shared their experience of TAMIS in redo pelvic surgery addressing complications or necessity for surgery following rectal resections and primary anastomosis and also in the context of pouch surgery. In a series of 17 patients, they described TAMIS use for redo anastomotic surgery in 13 and pouch problems in the remaining four. A majority of patients had chronic presacral sinus due to prior anastomotic dehiscence after low anterior resection, and pouch problems were due to efferent loop syndrome, obstructive pouch polyp, voiding disorder, recurrent cuffitis. Using a hybrid technique of transanal/transabdominal approach for most (15/17), feasibility was defined as the ability to complete rendezvous from transanal to transabdominal level (at seminal vesicles/anterior curvature of neorectum in women) beyond the anastomosis[43]. Whereas for those with sole TAMIS procedures (2/17) feasibility was defined as the ability to perform safer dissection with better visualisation of the dehisced anastomosis. This increased visibility is proposed to be one of the likely benefits of the TAMIS approach in redo pelvic surgery, with supposed lower risk of neurovascular injury, however this remains yet to be proven[43]. The authors proposed the merits of TAMIS in the context of redo surgery of the above nature to be judged on feasibility and complication rate, in view of the absence of oncological issues. Another potential anastomotic problem that can be addressed by this platform is the treatment of completely occluded anastomotic strictures, with incision of the blind end with electrocautery following confirmation of proximal lumen with contrast[44].

Pelvic exenterative surgery

The TAMIS platform has been applied to exenterative surgery in the context of advanced rectal cancer, with case reports by two groups of authors, both from Japan[45-47]. The technique described involves a hybrid transabdominal/transanal approach with the use of TAMIS access port following incision of the perianal skin incision and subsequent perirectal tissue and muscles dissection until the abdominal cavity is encountered[45]. The platform is proposed to facilitate the pelvic dissection with removal of the pelvic organs within the visceral pelvic fascia[46]. Clearly, evidence is very limited at this stage, however, there may well be future adoption of this technique in view of the proposed advantages of increased visibility, reduced blood loss and smaller perineal wounds with the TAMIS approach[46]. As the series are small and assessing feasibility there is no formal comparison available with the conventional open technique, and the oncological outcomes and long term safety of this technique will need to be evaluated in future studies.

ROBOTIC TAMIS

Robotic transanal surgery is one of the developments which have arisen from the natural evolution of TAMIS. It was initially described in a cadaveric model by Atallah and colleagues[48] and was proposed at the time as a potential tool to counteract some of the limitations of using standard laparoscopic instruments and approaches via a TAMIS platform. In particular, limitation of operative navigation in the confined rectal lumen, and the resultant restriction in instrument working angles *vs.* camera angle can make transanal surgery challenging. Proposed advantages of combining robotic technique with the TAMIS platform include greater precision for dissection and ease of intraluminal suturing of the surgical defect compared to standard TAMIS[5]. Atallah *et al.*[49] subsequently demonstrated the option of using the da Vinci surgical robot to perform TAMIS as an option for local excision of rectal lesions, later going on to perform a pilot study for transanal TME using the robotic-TAMIS platform[49]. The feasibility and safety of these approaches have been confirmed in other cohort series from various groups in Europe and America, demonstrating its feasibility and safety in both local excision and taTME[7,49-54]. The pioneers of this technique also describe its use in the repair of complex fistula, specifically in the repair of three rectourethral fistulae and 1 anastomotic fistula, using the robotic TAMIS platform for suture closure of the fistula and flap construction of the rectal wall[53]. The robotic TAMIS use is still very much in its infancy, and studies are currently experimental, demonstrate feasibility with anecdotal reports of advantages in ergonomics, tremor elimination, motion scaling and instruments with multiple degrees of freedom[55]. However, the financial implications as well as the increased set up time of robotic techniques may well serve as a significant counteraction to widespread use. As this modality evolves with technology, further studies will be required to determine whether it offers significant patient benefit.

DISCUSSION

There has been a rapid explosion in the TAMIS platform, with widening use for intraluminal and extraluminal pelvic surgery. The reported ease of access to the rectum and pelvis lends use to various additional applications as described. Furthermore, the rapid development of compatible instruments, ports, and equipment is allowing further refinement to improve the technical approach to this complex area of colorectal surgery. The cost savings, potentially shorter learning curve for trained colorectal surgeons and increased incorporation into surgical training in comparison to TEM[56], are likely to stimulate an increase in procedures being performed using the TAMIS modality. Comparative studies will however be required to address benefit between these two techniques as none currently exist.

Martin-Perez *et al.*[10] described TEM surgery (equipment by Richard Wolf GMBH, Knittlingen, Germany) as being born out of the need to improve on conventional transanal excision with a Park's retractor. TEM was soon followed with reports of TEO (equipment by Karl Storz GmbH, Tutlingen, Germany), which similarly uses a rigid rectoscope, but employs a 2-D high definition camera compared with TEM's 3-D and thus obviating the need for specially designed instrumentation and equipment as is required with TEM. When compared with TEM, TEO has been reported to offer similar results in terms of quality of surgical resections and surgical difficulty, however, there is limited published evidence on its use[57-60]. TAMIS was born out the need to make transanal surgery more accessible to all, cost-effective and with a more translatable learning-curve. The spectrum of pathology that can be managed with TAMIS has already broadened from excision of intraluminal small rectal lesions to a full TME[43]. Short-term outcomes for TaTME show shorter operative times, lower readmission rates, and acceptable morbidity and mortality with satisfactory oncological resection quality[5,28,61]. As with most pathology a nuanced approach is necessitated and TAMIS offers that for low lying rectal lesions and has particular benefit in complex cases such as in obese male patients. Here TAMIS offers visibility and technical advantage for a presumed narrow pelvis and is advantageous where exposure to the distal rectum from the abdominal approach can be challenging[5]. The improved transanal visibility and exposure as well as proposed technical advantage has led to a breadth of applications, with increasing use in benign pathologies including repair of recto-urethral fistula, ligation of distal rectal haemorrhage, resection of tail-gut/duplication cysts, removal of rectal foreign body[62,63]. Where uncertainty or complexity exists pre-operative planning and rehearsal with imaging adjuncts has been shown to be beneficial and can aid guide surgery in complex cases[64]. The utility of novel imaging techniques (e.g., 3D imaging, stereotactic surgery) in preoperative surgical planning and intraoperative mapping has been recently showed both in benign conditions and cancer[65-69]. This might allow a truly personalized approach with TAMIS proctectomy, where the extent of the TME can be adapted to disease features and patient needs.

Long-term oncologic outcomes and controlled trials of the technique are needed to guide further use in clinical practice. As the interest and uptake of this exciting new platform continues to rise exponentially[70], further prospective and comparative studies will be beneficial in evaluating this platform and shaping its role. Together with following international guidelines and recommendations, surgeons willing to offer their patients the option for TAMIS need to follow the training pathways and accreditation which have been set for the safe implementation of the technique into clinical practice. Under this light, a critical role is also played by honest participation into International registries, which can capture a wider, real-life perspective about performance, safety and patient-relevant outcomes of surgical procedures. Consensus exercises will also be useful in defining patient selection criteria and indications for its use in the armamentarium of colorectal surgery.

DECLARATIONS

Authors' contributions

Conceptualised the topic and oversaw direction of narrative: Warusavitarne J
Drafted the manuscript: Adegbola SO
Performed literature review, prepared the manuscript: Adegbola SO, Sahnan K, Pellino G
Revised the manuscript critically, prepared the final version: all authors

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Mini-invasive Surgery

Review

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Enhanced recovery after surgery in liver surgery

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Abstract

Enhanced recovery after surgery (ERAS) or fast-track surgery protocols, have been implemented across surgical fields with positive impact on outcomes. These protocols represent a standardized and evidence-based multimodal perioperative strategy founded on a series of measures aiming to attenuate the physical and psychological stress responses to surgical insults, and to potentiate the postoperative rehabilitation of patients. The successful adoption of ERAS protocols in various specialties enabled its gradual acceptance in the complex field of liver surgery. Even though many elements have been adapted especially from colorectal surgery, a few elements of ERAS protocol are unique to liver surgery. The goals of enhanced recovery can be achieved with efforts beginning at the first interaction on outpatient basis. Core elements of this multidisciplinary effort include pre-operative counseling, shortened preoperative fasting, no pre-anesthetic medication, targeted antimicrobial prophylaxis and early withdrawal, preventing and treating of postoperative nausea and vomiting, minimally invasive approaches, avoidance of postoperative nasogastric decompression, preventing hypothermia, optimal perioperative fluid management, selective use of abdominal drains, early urinary catheter removal, optimal pain control, early oral feeding and mobilization. The available evidence from recent randomized controlled studies and meta-analyses comparing ERAS programs with traditional care in liver surgery suggests that length of hospital stay is shortened without increasing morbidity, mortality or readmission rates.

Keywords: Liver surgery, hepatic surgery, enhanced recovery after surgery, fast track, enhanced recovery

INTRODUCTION

Surgery alters the body physiology and defense mechanisms resulting in a catabolic state with impaired immunity, gut motility and respiratory physiology. These post-operative physiologic changes stem from metabolic, inflammatory or immunological responses and are thought to be primarily responsible for morbidity[1]. Mechanistically, initiation of surgical stress response is primarily due to afferent nerve im-pulse combined with release of humoral substances [such as prostaglandins, kinins, leukotrienes, IL-1 and tumor necrosis factor (TNF)]. This phenomenon is amplified by factors including semi-starvation, infection and hemorrhage[2]. The neural pathway is probably most important in releasing the classic endocrine catabolic response, while associated release of humoral factors is important for the hyperthermic response, changes in coagulation and fibrinolysis, immune function and capillary permeability[1,2]. No wonder, attenuation of surgical stress response is dependent upon the technique of analgesia and afferent neural blockade with local anesthetic, with epidural being the most effective technique[1]. The introduction of effective neural blockade and use of epidural analgesia has been found to mitigate the metabolic response to surgical stress, but has a less important effect on inflammatory or immunologic responses. On the contrary, minimally invasive surgery reduces the inflammatory response and immune suppression, while leaving the metabolic response mostly unaltered[1].

Even though the concept of bundling perioperative treatments to improve outcomes was developed in the early 90' and known as "Fast-Track" surgery, the enhanced recovery after surgery (ERAS) protocol was developed in Europe in 2001[3,4]. This last involved a more comprehensive multidisciplinary and multimodal approach with the main end-point of enhancing the quality of recovery by attenuating the perioperative surgical stress and improving the response to stress rather than just accelerating the speed of recovery[4]. Initially employed in colorectal surgery, it led to tremendous improvement in patient outcomes following surgery. This was later adopted by other surgical specialties including liver surgery. No wonder, many recommendations pertaining to ERAS in liver surgery arise from the experience in colorectal surgery[5]. However, there has been an increased need to develop liver specific programs to optimize ERAS protocols and outcome parameters given that features such as hepatic reserve evaluation, surgical complexity and risk of post-hepatectomy liver failure are unique to liver surgery. Naturally, many strategies employed to enhance recovery after liver surgery are similar to other surgical fields, including perioperative measures as well as postoperative recovery standardization [Table 1]. After Mackay and O'Dwyer[6] reported their initial enhanced recovery protocols for liver resection, few ERAS protocols for liver surgery have been published, and data is limited mostly to observational studies and few randomized controlled trials (RCT)[7-9]. In addition, there is scarce data comparing ERAS programs with conventional liver surgery protocols, and meta-analyses including RCTs suffer from inadequate disclosure of randomization techniques[9]. The subjective nature of end points (i.e., time to flatus) and the heterogeneity in outcome measures between studies lead to inherent imprecise data [i.e., length of stay (LOS), where the patient may be fit for discharge but stay in hospital due to logistic reasons]. Primary surgeon experience, baseline patient characteristics and selection criteria may also significantly impact the validity of results. Hence, even though there is a growing body of evidence in favor of ERAS application in liver surgery, further studies are required to determine the most effective ERAS protocol for this particular field. The purpose of this review is to summarize the current scientific evidence on the most important elements of an ERAS program in liver surgery and the outcomes associated with the application of this protocol compared to traditional care.

KEY COMPONENTS OF ERAS PROTOCOLS IN LIVER SURGERY

Implementation of the complete set of traditional core elements of ERAS protocols is rarely seen in referral liver surgery centers[10]. Although pre- and perioperative elements have a good adherence, compliance is especially poor for the postoperative phase elements[10]. This may be due to the fact that at least 7 out of 23 classical ERAS items validated for colorectal surgery have not been studied in liver surgery yet, and it is currently unclear whether they can be extrapolated for liver surgery[5]. However, some have been considered of outmost importance for liver surgery in recent meta-analyses and a consensus guideline from the international ERAS Society[5,9]. Specifically, pre- and intraoperative fluid restriction and no routine nasogastric tubes (NGTs) postoperatively have been considered significant for liver surgery[9]. On the contrary, elements such as preoperative oral mechanical bowel preparation and postoperative stimulation of bowel movement are not considered indicated in liver surgery[5].

Table 1. Core elements for enhanced recovery after surgery protocols in liver resections

Pre-operative	Peri-operative	Post-operative	At discharge
• Education, counselling and exercise • No bowel preparation • No preanesthetic medications • Carbohydrate loading 2 h prior surgery • Minimal fasting (2 h)	• Antibiotic prophylaxis • Thromboembolic prophylaxis • Epidural analgesia • Short-acting i.v. anesthetic agent • Prevention of hypothermia • Optimal fluid balance no abdominal drains or early removal • Minimal incisions	• No nasogastric tube • Selective ICU transfer • Multimodal analgesia • Early removal of Foley's catheter • Early enteral intake • Early ambulation • Early withdraw of i.v. fluids • Early restoration of normal diet • Glucose Control PONV prophylaxis	• Normal or decreasing serum bilirubin • Good pain control with oral analgesia only • Tolerance of solid food • No i.v. fluids • Mobile independently or at the preoperative level • Willingness to go home • Normal body temperature • No incision infection

ICU: intensive care unit; PONV: postoperative nausea and vomiting

Preoperative information and counselling

Fear and stress are common prior to surgery. Hospitalization is a stressful event that disturbs the physical and psychological wellbeing of a patient. Stress due to apprehension of surgery leads to activation of sympathetic axis and adrenaline overdrive. Increased cortisol and catecholamine production can significantly impact the healing process and particularly the initial inflammatory phase[11]. Although no high level evidence exists certifying the beneficial impact of preoperative counseling and education on outcomes, there is no doubt that education aids such as brochures, leaflets and online information help the patients in decision making and enhance the validity of informed consent[5]. Also, the engagement of visual media regarding the recovery process and postoperative expectations improves overall compliance with feeding and physiotherapy, hence reducing morbidity[12]. Whatever approach is employed, detailed information about the natural history of disease, surgical procedure, anesthesia, expected course of recovery and complications reduces stress and anxiety related to the procedure, which positively impacts postoperative outcomes. Earlier return of gastrointestinal (GI) motility has been shown in patients who received preoperative instruction compared to those who merely received information and reassurances[13]. Therefore, adequate counseling and communication with empathy may be all that is required sometimes to relieve postoperative ileus during the post-operative period[14]. Although there are no specific studies evaluating the therapeutic effect of preoperative counseling and patient education before liver surgery, it is strongly recommended for any ERAS protocol to include thorough preoperative information and counseling in order to allay patients' fear and reduce psychological stress.

Preoperative fasting

The concept of overnight fasting before surgery to ensure an empty stomach and avoid pulmonary complications has been decisively challenged in recent years. Prolonged fasting leads to perioperative insulin resistance, fever, symptoms like malaise, hunger, thirst, nausea and increases patients' anxiety[15]. Fasting guidelines before surgery are based on gastric physiology and expert opinion, as there is limited evidence that they improve outcomes. Clear liquids and gastric secretion move rapidly out of the stomach, and even though glucose containing fluids leave the stomach more slowly, after 90 min the stomach is empty of clear liquids regardless of type[16]. Gastric residual volume averages about 25 mL in patients fasted overnight prior to surgery, and clear liquids intake up to 2 h before surgery does not seem to affect this residual volume[17,18]. In a Cochrane database systematic review, Brady *et al.*[19] have shown that a liberal fluid fasting protocol does not increase the risk of aspiration or morbidity as compared to a conventional mid night fasting policy. Surgical insult following overnight fasting results in an exaggerated catabolic response that causes insulin resistance and prolongs recovery[2]. In fact, insulin resistance is a central metabolic change during surgical stress that is directly proportional to the magnitude of the operation and leads to hyperglycemia in non-diabetic patients[2]. As a consequence, various endocrine and inflammatory systems are stimulated. This results in an exacerbation of the existing postoperative catabolic state with marked loss of body fat and protein stores[20]. Given that postoperative insulin resistance has been associated with poor pain control, increased morbidity, and increased length of hospital stay after surgery, several studies have examined the impact of preoperative carbohydrate drink on patient well-being[2]. A review of 17 RCTs including 1445 patients concluded that patients receiving carbohydrates have reduced LOS, less perioperative insulin resistance and experience less fever, hunger, thirst, nausea and anxiety[21]. Hausel *et al.*[22] investigated the impact of carbohydrate loading on postoperative nausea and vomiting (PONV) in 172 patients undergoing elective laparoscopic cholecystectomy. Within the first 24 h after surgery, the carbohydrate fed group experienced significantly lower incidence of PONV. Yet, other studies have not reported such beneficial effects[23]. Mathur *et al.*[24] conducted a double-blind placebo RCT in 2009 to study the effect of preoperative carbohydrate drink on clinical outcomes after colorectal surgery and liver resection. The study however, did not observe any beneficial effects in LOS, oral intake or postoperative infections. Despite some controversy, carbohydrate loading has a solid physiologic foundation which is supported by several studies[5]. Thus, incorporation of such strategies helps in patient's enhanced recovery, more so in the light of the fact that insulin resistance affects liver regeneration and might therefore have the potential of further delaying the recovery[2]. Overall, although preoperative fasting does not need to exceed 6 h for solids, a judicious recommendation for patients being operated at first time on the morning is to allow a normal meal the night before and continue carbohydrate liquids up to 2 h before induction of anesthesia.

Antimicrobial prophylaxis

Surgical site infection (SSI) is the most common postoperative complication after high-risk surgery, which increases both hospital stay and treatment costs[25]. Incidence of SSI after liver resection ranges between 2% and 15%, and has significant impact on LOS, morbidity and mortality[26,27]. Even though liver surgery is considered a clean contaminated surgery, it is categorized as contaminated surgery when combined with extrahepatic bile duct resection due to the possibility of biliary or enteric spillage during surgery. In such scenarios, bile is almost always (up to 75%) contaminated due to preoperative biliary drainage[28]. In addition, invasive nature of major hepatic resection and inevitable surgical field contamination has lead to the empirical use of prolonged antibiotic prophylaxis among surgeons. This practice, however, ends up increasing bacterial resistance and prolongs patient recovery. To date, three RCTs on postoperative antibiotic prophylaxis in patients undergoing hepatectomy without extrahepatic bile duct resection have been reported. Although only one of these RCTs has supported prolonged prophylaxis based on significant difference in the incidence of signs of infections or systemic inflammatory response syndrome, the incidence of infection did not differ among all RCTs[29-31]. In a more recent RCT by Sugawara *et al.*[32], it was found that two-day administration of antibiotic prophylaxis is sufficient for patients undergoing complicated major hepatectomies with extrahepatic bile duct resection. Various other methods to reduce infectious complications have been attempted, including the use of pre- and pro-biotics, with no strong evidence of their efficacy[33]. In summary, it is recommended to administer a single dose of intravenous antibiotics before skin incision, of the type recommended by a local infectious committee. Postoperative "prophylactic" antibiotics are not recommended, with the exception of simultaneous bile duct resection in patients with a biliary drainage, where prophylaxis should be selected on the basis of preoperative surveillance bile cultures and discontinued on postoperative day (POD) 3, unless evidence to the contrary is shown.

Antithrombotic prophylaxis

Despite the common belief that liver resection impairs coagulation, increasing the risk of bleeding and protecting patient from thromboembolism, hypocoagulability is rare after liver resections[34]. A study done in living donor hepatectomy showed that pulmonary embolism is not rare despite prophylaxis with low molecular weight heparin (LMWH)[35]. These clinical findings have been supported by thromboelastogram monitoring which shows a hypercoagulable state after liver resection due to imbalance in coagulation proteins[36,37]. Furthermore, major hepatectomy has been identified as an independent risk factor for pulmonary embolism[38]. A cohort study of 419 patients showed lower symptomatic postoperative venous thromboembolism if prophylaxis is initiated from day 1 after major hepatectomy[39]. One meta-analysis suggested continuing thromboprophylaxis for 4 weeks post-operatively, especially in patients bearing liver malignancies[40]. The combination of pharmacologic and mechanical prophylaxis, such as compressive stocking and intermittent pneumatic compression, may further reduce the risk in the high-risk group of patients[41]. In summary, routine prophylaxis with LMWH or unfragmented heparin should be initiated 2-12 h before surgery in major hepatectomies, restarted 8-12 h after surgery if there are no signs of bleeding, and discontinued once the patient is discharged[5]. Given the absence of high-level evidence, extended thromboprophylaxis (28 days) should be considered only in selected patients with high-risk scores.

Minimally invasive approach

Even though none of the four incisions used for open liver surgery (median, Chevron, Mercedes-benz and Makuuchi) has shown to offer any advantages over the others and perioperative complications remain comparable, mini-invasive approaches have consistently demonstrated a substantial benefit with regards to patient recovery over the open approach. The central concept of surgical stress response attenuation orbits around the minimally invasive approach. Laparoscopic liver resection (LLR) was introduced in the early 1990's[42-44]. Over the years, the many advantages of LLR have became widely accepted, with reduced intraoperative bleeding, shorter LOS, less pain, lower infection rates, earlier recovery and better quality of life (QOL)[45-51]. In addition, emerging data has now confirmed the safety and oncologic equivalence of the laparoscopic approach for both malignant liver lesions[48,52-54]. A recent meta-analysis by Liu *et al.*[55] found that laparoscopic left lateral sectionectomy had significantly better results regarding blood transfusion, blood loss, total morbidity and LOS compared to the open approach. In fact, while major LLRs are still under development, minor LLRs including left lateral sectionectomy have become standard practice nowadays[47,48,55]. With regards to ERAS protocols in LLR, Stoot *et al.*[56] reported from retrospective data a reduction in LOS from 7 days to 5 days when laparoscopy and ERAS program were combined. More recently, a propensity score-based analysis between the open and laparoscopic approaches from Ratti *et al.*[57] has found that the combination of a minimally invasive approach with a fast-track protocol allows a reduced rate of postoperative morbidity and satisfactory functional recovery, even in the setting of complex liver resections. Although laparoscopic surgery offers an additional advantage to ERAS protocols during postoperative recovery, adequate patient selection and surgeon expertise are key determinants of success[47,48]. Patients with lesions located in peripheral liver segments (Segments 2 to 6) that require minor resections (≤ segments) are considered the best candidates for this approach[47,48]. So far there are no studies assessing robotic liver surgery within ERAS frameworks.

Prophylactic nasogastric intubation

Pathogenesis of postoperative ileus as demonstrated by Wangensteen[58] arose from excess of swallowed air, which can be relieved by NGT insertion. However, a NGT has been consistently associated with higher pulmonary complications and this may be due to several reasons[59]. First, it may be due to the incomplete closure of the glottis during cough hence leading to the accumulation of secretions, with increased risk of atelectasis and infection. Secondly, it acts as a conduit for transfer of bacteria from the oropharynx to the lungs. Thirdly, NGT also may cause diaphragmatic dysfunction through reflex mechanisms[60,61]. Time to passage of flatus and return to oral intake are delayed due to NGT, and around 70% of patients experience marked discomfort limiting mobility with increased nursing care[62-64]. Furthermore, NGT is also associated with laryngeal injury, esophagitis, pharyngitis, otitis, electrolyte losses, aerophagia and rhinosinusitis[65-67]. A Cochrane review concluded that routine prophylactic use of NGT in general abdominal surgery can increase pulmonary complications and delay bowel function, therefore recommending its selective use[68]. With regards specifically to NGT use after liver resections, two recent RCTs have confirmed the increased risk of complications and the absence of any advantages after elective liver surgery[59,69]. In summary, even though NGT decompression may be necessary during surgery, immediate on-table removal after surgery is strongly recommended as it has been proven to be safe and associated with better outcomes and an improved peri-operative experience for the patient[5].

Prophylactic drainage

An intense debate about the value and risk of prophylactic drainage in liver resections was raised in 2004 after a meta-analysis provided a strong ground to omit routine prophylactic drainage after major abdominal surgery[70]. Recent data from RCTs and large retrospective studies suggest that there is no evidence to support routine drain use after uncomplicated liver resections without bilio-enteric anastomosis[71,72]. Furthermore a routine use policy may even lead to an increased risk of complications and 30-day readmissions in major hepatectomy[73-75]. Overall, prophylactic drainage tubes should be used selectively and early removal is recommended in the absence of complications in order to promote easier mobilization.

Postoperative mobilization and urinary catheter removal

Bed rest in critically ill patients or after surgery can lead to muscular atrophy, weakness, joint contracture, thromboembolism, insulin resistance, microvascular dysfunction, systemic inflammation, atelectasis and bed sores[76]. Early physical activity during recovery from surgery has beneficial effect on many aspects of physiological functions. Up to 85% of patients undergoing liver resection may be ambulatory by postoperative day 3[7]. In a study by Yip *et al.*[77], sitting out of bed by POD 1 ($P < 0.03$), walking by POD 3 ($P = 0.03$) and removal of urinary catheter by POD 3 ($P < 0.01$) were independently associated with successful completion of an ERAS protocol aiming at hospital discharge within 6 days after surgery. Delay in removal of urinary catheter is enough to prolong hospital stay. In a RCT, Zaouter *et al.*[78] demonstrated catheter removal on POD 1 even with epidural analgesia had lower urinary infection rate and similar re-catheterization rates. A recent RCT by Ni *et al.*[79] including 120 patients has shown that patients undergoing liver resection who perform early postoperative ambulation have statistically significant faster return of bowel function and shorter LOS, without increased risk of complications. Hence, early ambulation could reduce economic burden and nursing workload as well as increase patient comfort and satisfaction. In summary, early "out of bed" mobilization with daily goals adjusted to each individual should start the day after liver resection, as it is both feasible and safe, and it leads to faster patient recovery.

Postoperative nutrition and early oral intake

Allowing patients orally early after major upper GI surgery does not increase morbidity. A RCT on 427 patients, 66 of which had undergone hepatic resection or hepaticojejunostomy, confirmed the advantages and safety of normal oral nutrition at will from postoperative day 1[80]. Use of laxatives resulted in earlier passage of stools but the overall rate of recovery was unaltered[81]. Parenteral nutrition should be only used in mal-nourished patients or patients expected to have a prolonged fasting (> 5 days) and longer recovery due to complications or otherwise[5]. In summary, it is nowadays recommended that patients under an ERAS protocol should be allowed liquids the morning after surgery and switched to normal food by the evening if there is a good tolerance there are no complications[5].

Postoperative glycemic control

Postoperative rise in blood glucose is expected due to deranged physiologic status of the body after major surgery. During hepatectomy, blood glucose levels shoot up sharply after Pringle maneouvre due to augmentation of glycogenolysis as a result of hypoxia[82]. In line with this concept, Hanazaki *et al.*[83] suggested that ischemic preconditioning may reduce the hyperglycemia caused by disturbances of hepatic glucose mechanism in association with ischemic reperfusion injury. Preoperative fasting combined with surgical stress response reduces liver glycogen stores and promotes insulin resistance with hyperglycemia[2]. Hyperglycemia is both a marker and cause of adverse outcomes both for diabetics and non-diabetic patients. The Interleukins released also cause insulin resistance either by suppressing insulin receptors tyrosine kinase activity or reduction of transmembrane glucose transporters expression, leading to hyperglycemia during early postoperative period[84]. It is therefore recommended to initiate insulin therapy early after liver resections in order to maintain normoglycemia[5].

PONV

Prevention and treatment of PONV is of utmost importance to allow early oral intake and keep the patient within an ERAS pathway. Risk factors include previous PONV, young female patient, nonsmoker, use of volatile anesthetic or opioids[5]. Given their favorable side effect profile, 5-HT3 antagonists such as Ondansetron, remain the treatment of choice[85]. Low dose dexamethasone has equivalent antiemetic action but has to be used with caution in diabetics[85]. Metoclopramide is a weak antiemetic and a dose of 10 mg may not effectively reduce PONV[86]. Therefore, the international ERAS society and the international consensus group on PONV recommend a multimodal prophylaxis including at least two antiemetic drugs to reduce PONV[5,87].

Perioperative steroid administration

Preoperative steroid in patients undergoing hepatic surgery is controversial and its use is limited. Although supported by experimental studies[88,89], beneficial effects stemming from its immunologic and anti-inflammatory action has not been consistent[90,91]. Although pre-operative steroid administration has not been associated with a reduction of post-operative complications in two recent meta-analysis of RCTs[90,91], it resulted in significantly lower levels of serum bilirubin and interleukins on POD 1[92]. The mechanism of action may be due to a protection against warm ischemia-reperfusion injury, lower IL's release, better tissue perfusion, stabilization of cell membrane and lower lysosomal protease release[93]. A negative effect of steroids in liver regeneration remains a concern, as IL-6 and TNF-α are important initiators of hepatic regeneration[94]. However, Glanemann *et al.*[95] showed in an animal model that steroids had no negative impact on liver regeneration. Although the use of preoperative steroids (methylprednisolone) can not be strongly recommended in liver surgery, they may be used only before hepatectomy in non-diabetic patients with normal liver parenchyma in order to decrease liver injury and intraoperative stress.

OUTCOMES OF ERAS PROTOCOLS COMPARED WITH TRADITIONAL CARE

In the inaugural experience with a multimodal ERAS program after open liver surgery, Van Dam *et al.*[7] reported a significant reduction in the LOS without increasing morbidity or mortality. Many later retrospective studies and meta-analyses comparing ERAS with traditional care have confirmed the safety and feasibility of ERAS in liver resection[96-98]. A recent meta-analysis by Wang *et al.*[9] showed that hospital stay was significantly shorter for ERAS patients in both RCTs and non-RCTs, being reduced by a mean of 2.65 days and 1.81 days, respectively ($P < 0.001$). This benefit was increased if laparoscopic surgery was applied, with a mean reduction of 3.64 days ($P < 0.001$)[9]. Time to bowel function recovery has been consistently found significantly shorter when an ERAS protocol is applied[9,99]. With regards to morbidity, a meta-analysis of 4 RCTs found that complications were significantly reduced in ERAS patients compared to traditional care patients (20.9% *vs.* 31.4%; $P = 0.02$)[99]. This was later confirmed by Wang *et al.*[9], who found significantly less overall morbidity in both RCTs and non-RCTs (OR = 0.57 and 0.66 respectively; $P = 0.01$). However, when categorized according to the Dindo-Clavien classification, although ERAS group had significantly fewer grade I complications (RR = 0.51; $P = 0.003$), there were no differences in grade II-V complications (RR = 0.94; $P = 0.80$)[100]. Similarly, a RCT by Jones *et al.*[97] found a significantly reduced rate of medical complications (7% *vs.* 27%; $P = 0.02$), but not surgical complications (15% *vs.* 11%; $P = 0.612$). In addition, three meta-analyses of RCTs found no significant differences regarding 30-day mortality and readmission rates between ERAS and traditional care approaches[9,101,102]. With regards to QOL evaluation, two RCTs have found a statistically significant improvement in QOL by one month after surgery in ERAS patients[98,103]. Finally, although the benefits in outcomes of ERAS protocols have been translated in significant cost saving in colorectal surgery, from around $2,800 to $5,900 per patient, this has not been widely confirmed in liver surgery yet[4]. Although a recent retrospective cost-benefit analysis of ERAS in liver surgery from Switzerland found a total mean cost reduction of €3,080 per patient compared to traditional care, this difference did not reach statistical significance ($P = 0.467$)[104]. The main outcomes of ERAS protocols reported in the literature are summarized in Table 2.

Table 2. Outcomes of enhanced recovery after surgery protocols in liver resections

Ref.	Year	Study design	*n*	Length of stay, days (Range)	Morbidity	Mortality	Results compared to TC
Spelt *et al.*[96]	2011	Review	130	5-7	15%-46%	0%-1.8%	Reduced LOS
Jones *et al.*[97]	2013	RCT	46	4	7%	2%	Reduced LOS and morbidity Improved QOL
Ni *et al.*[98]	2013	RCT	80	5.2	30%	0	Reduced morbidity, PONV, ileus and LOS Lower CRP
Lei *et al.*[99]	2014	Meta-analysis of RCT's	187	4-9.2	20.9%	0	Reduced time to flatus, morbidity, LOS
He *et al.*[103]	2015	RCT	48	4-8	14.6%	0	Reduced LOS, time to flatus and cost Improved QOL
Ni *et al.*[100]	2015	Meta-analysis of RCT's	354	5	15.5%	0	Reduced morbidity, ileus and LOS
Liang *et al.*[105]	2016	RCT	80	6.2	22.5%	0	Reduced LOS, morbidity and cost
Li *et al.*[101]	2016	Meta -analysis	477	6-10	29.7%	0.02%	Reduced LOS
Wang *et al.*[9]	2017	Meta-analysis	1297	2.5-10	28.4%	0.49%	Reduced morbidity, LOS, cost and blood loss
Rouxel *et al.*[102]	2018	Review	254	4-6.9	7%-24%	0.004%	Reduced morbidity and LOS

RCT: randomized controlled trial; TC: traditional care; LOS: length of hospital stay; QOL: quality of life; PONV: postoperative nausea and vomiting; CRP: C-reactive protein

Figure 1. Summary of the enhanced recovery after surgery protocol applied at our institute. LMWH: low molecular weight heparin; PPI: proton-pump inhibitor; CVP: central venous pressure; CUSA: cavitron ultrasonic surgical aspirator; POD: postoperative day

CONCLUSION

ERAS programs represent a standardized and evidence-based multimodal perioperative pathway founded on a series of measures aiming to attenuate the physical and psychological stress responses to surgical insults, potentiating postoperative rehabilitation of patients. Increasing evidence demonstrates that the application of ERAS in the field of liver surgery leads to an improvement in LOS, morbidity, patient satisfaction and a trend towards less hospital costs compared to traditional care. These benefits are leading to an increase adoption of various elements of ERAS protocols as part of modern surgical practice in liver surgery referral centers worldwide, including our institute [Figure 1]. Core elements of this multidisciplinary effort include adequate pre-operative patient education and counselling, shortened preoperative fasting with carbohydrate loading, judicious use of pre-anesthetic medication, prophylaxis against venous thromboembolism, targeted antimicrobial prophylaxis and early withdrawal, preventing and treating of PONV, minimally invasive approach, avoidance of postoperative nasogastric decompression, preventing hypothermia, optimal perioperative fluid management, selective use of abdominal drains, early urinary catheter removal, optimal pain control, early oral feeding and mobilization. Given the strong evidence suggesting that strict adherence to ERAS protocols is paramount for their successful implementation, continuous local audit of compliance has also become a key element of the approach[2,5]. Even though there is a growing body of evidence in favor of ERAS application in liver surgery, further studies are required to determine the most effective ERAS protocol for this particular field.

DECLARATION

Authors' contributions

Contributed significantly to the work, read the manuscript, attest to the validity and legitimacy of the data and its interpretation: Kumar N

Contributed significantly to the work, read the manuscript, revised the manuscript, attest to the validity and legitimacy of the data and its interpretation: Jha SK

Conceptualised the review, contributed significantly to the work, read the manuscript, attest to the validity and legitimacy of the data and its interpretation: Negi SS

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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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Quality of life after minimally invasive surgery for rectal cancer

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Abstract

Traditional open surgical technique for rectal cancer is associated with significant morbidity and impact on quality of life. Multiple structures are at risk during total mesorectal excision, which may have profound impact on sexual function, and urinary and fecal continence. In addition, having a temporary or permanent ostomy can have a significant effect on overall well-being. Patients have reported post-operative problems such as chronic wounds, poor body image, inhibited work and social function. Minimally invasive surgery (MIS) is an evolving component of colon and rectal cancer treatment that may have benefits over open surgery. The increasing role of laparoscopy for colon and rectal cancer has been associated with decreased morbidity, improved pain control, and reduced length of stay. However, laparoscopic surgery in rectal cancer remains technically difficult due to the inherent limitations of operating in the pelvis. Robotic surgery is a newer method for treating rectal cancer developed to overcome these limitations. Transanal endoscopic microsurgery and transanal MIS are techniques to achieve local excision, avoiding proctectomy in select patients, potentially improving functional outcomes. Transanal total mesorectal excision is an even newer technique to facilitate dissection of low rectal cancers. Controversy remains about equivalence in oncologic outcomes when these MIS approaches are used for rectal cancer. Even more unclear is the effect of MIS approaches on quality of life and how they compare to open surgery. This review discusses the most current evidence on the impact of various MIS techniques on quality of life after rectal cancer surgery.

Keywords: Quality of life, rectal cancer, minimally invasive surgery, laparoscopic, robotic, transanal endoscopic microsurgery, transanal minimally invasive surgery, transanal total mesorectal excision

INTRODUCTION

The introduction of laparoscopy in the 1990s revolutionized the practice of surgery[1]. Minimally invasive surgery (MIS) forever changed a breadth of specialties including not only gynecology, urology, and general surgery, but also colorectal surgery[2]. The benefits of MIS are innumerable, including a reduction in pain and narcotic use, shorter length of stay, and earlier return to work compared to conventional open surgery[2,3]. These tremendous improvements in functional outcomes have translated into an improved quality of life. Given the significant reduction in overall complications and costs, MIS has become the standard of care for multiple benign disease processes[2].

In the setting of malignant disease, MIS must achieve equivalent oncologic outcomes in survival and local control compared to open surgery. The colon cancer laparoscopic or open resection (COLOR) trial and the United Kingdom Medical Research Council (MRC) conventional *vs.* laparoscopic-assisted surgery in colorectal cancer (CLASICC trial) demonstrated laparoscopic surgery for colon cancer to be as effective as open surgery in terms of oncologic outcomes and preservation of quality of life[1,4]. Since then, other multicenter prospective controlled studies have further supported the use of laparoscopic surgery as a safe and effective alternative to open surgery in the treatment of colon cancer, with five to ten year follow-up analyses showing equal if not better oncologic and functional outcomes[4,5].

Despite the strong evidence for the treatment of colon cancer, the evidence in support of MIS as a standard for rectal cancer is not clear. Furthermore, the definition of MIS for rectal cancer is broad and continues to evolve with the incorporation of multiple platforms for treatment including robotic-assisted approaches, transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), and transanal total mesorectal excision (TaTME). Given the unique anatomic location of rectal cancers deep in the pelvis, the pelvic blood vessels, autonomic nerves, and anal sphincters are all at high risk for injury during surgery. Open surgery is associated with significant rates of postoperative sexual and urinary dysfunction ranging from 20% to 100% leading to a profound effect on overall well-being[6,7].

There has been more emphasis on measuring "quality of life" after oncologic resection in recent years. This perhaps is rooted in the The World Health Organization's definition of health as "a state of complete physical, mental, and social well-being and not merely the absence of disease." Quality of life may depend on many variables including patient factors (e.g., age, culture), tumor factors (e.g., size, distance from anal verge) and treatment factors (e.g., need for ostomy, radiation, type of surgery).

Early studies on minimally invasive approaches for rectal cancer have not all shown equivalent oncologic outcomes, and it is still unclear what the effect of these approaches is on functional outcomes. Clinicians need to counsel patients on the potentially profound effects on quality of life with any approach. In this review, we examine the evidence on the quality of life outcomes of MIS in treating rectal cancer.

SEARCH STRATEGY

The PubMed database was queried for keywords "rectal cancer", "quality of life", "functional outcomes", "minimally invasive surgery", "laparoscopic", "robotic", "transanal endoscopic microsurgery", "transanal minimally invasive surgery", and "transanal total mesorectal excision". Clinical trials, review articles, and meta-analyses in English that measured patients' quality of life after rectal cancer were included for review. Studies were excluded if patients were not distinguished between colon and rectal cancer in the study.

QUALITY OF LIFE ASSESSMENT

The assessment of quality of life depends on patient-reported outcomes conducted through questionnaires. The most common questionnaires include the non cancer-specific instrument, the medical outcomes study short form general health survey of 36 questions (SF-36); a cancer-specific instrument, the European organization for research and treatment of cancer quality of life questionnaire EORTC QLQ-C30 version 3.0; and the two colorectal cancer-specific instruments, the EORTC colorectal quality of life questionnaire QLQ-CR38 and QLQ-CR29[8-12]. The SF-36 questionnaire is a generic health survey that can be applied across different diseases and treatment groups. It seeks to capture the physical, mental, and social health of patients through 36 questions. The EORTC quality of life questionnaires were developed by a broad range of professionals involved in the care of cancer to provide a multidimensional assessment of health for the cancer patient that could be self-administered and applicable across a range of cultural settings. The QLQ-C30 questionnaire consists of 30 items divided into functional scales of physical, emotional, cognitive, and social function; a symptom scale, and a global health scale. The symptom scales include assessments on pain, fatigue, appetite, insomnia, and emesis. The EORTC QLQ-CR38 and QLQ-CR29 colorectal cancer specific questionnaire addresses issues specific to colorectal cancer patients related to gender, urinary and fecal incontinence, and problems associated with having a stoma.

The International Prostatic Symptom Score (IPSS) questionnaire measures urinary incontinence and the International Index of Erectile Function (IIEF) questionnaire measures male sexual dysfunction. IPSS evaluates urinary issues such as frequency, urgency, nocturia, dysuria, and straining during micturition. The international consultation on incontinence male/female lower urinary tract symptoms were also used in some studies[13-16]. The IIEF-5 assesses various aspects of male sexual function including erection, penetration, ejaculation, desire, and overall enjoyment[17]. The female sexual function index (FSFI) questionnaire assesses female sexual function, exploring aspects of sexuality including desire, arousal, lubrication, satisfaction, pain, and confidence[18].

LAPAROSCOPIC SURGERY FOR RECTAL CANCER

Laparoscopic surgery is now more utilized than open surgery for colon cancer due to favorable short-term outcomes related to smaller incisions, including less pain, reduced blood loss, and improved recovery time[19]. Furthermore, the use of the laparoscope allows for the projection of a high resolution, magnified, well-illuminated image of the operative field on multiple monitors. The ten-year outcomes of the COLOR trial demonstrated equivalent oncologic outcomes between laparoscopic and open surgery for colon cancer in terms of overall survival, disease-free survival, and local recurrence[20]. The purported advantage of laparoscopic surgery in rectal cancer is better visualization of the deep pelvis and possibly a more accurate dissection for a total mesorectal excision (TME) than in open surgery. However, laparoscopy in the pelvis is technically difficult, especially in obese patients with low tumors or narrow pelvises. Maintenance of a stable camera view and adequate retraction is not often ergonomic, leading to a loss of exposure from surgeon and assistant fatigue.

Multiple single center studies have reported quality of life outcomes after laparoscopic surgery for rectal cancer. In 2006, a single center prospective longitudinal study conducted in the Netherlands examined the quality of life and sexual function of 51 patients with rectal cancer who underwent either a laparoscopic low anterior resection (n = 38, 75%) or laparoscopic abdominoperineal resection (n = 13, 25%)[20]. These patients were surveyed with three quality of life questionnaires: SF-36, EORTC QLQ-C30, and EORTC QLQ-CR38. The questionnaires were given preoperatively, and postoperatively upon discharge, and at 3, 6, and 12 months. The study found that although physical function, social function, vitality, and pain scores were all worse at the time of discharge compared to baseline scores, all of these measures improved to baseline by three months and were maintained up to one year postoperatively. Improved mental function compared to baseline was noted at three months and emotional function improvement was also noted at one year. Patients also reported an improvement in global quality of life at one year after surgery compared to their baseline preoperative level. This improvement included alleviation of symptoms of fatigue, pain, appetite loss, and diarrhea. There was no comparison group to open in this study[20].

Braga *et al.*[21] in 2007 conducted a single center randomized control trial in Italy comparing 168 patients (83 laparoscopic *vs.* 85 open) for rectal cancer < 15 cm from anal verge and demonstrated improved general health, physical functioning and social functioning in the laparoscopic group at 3, 6, and 12 months after surgery. In a single center prospective cohort study in India examining sexual and urinary dysfunction in male patients after laparoscopic TME, 34 patients with low (0-6 cm from anal verge) to mid (7-12 cm from anal verge) rectal cancers who underwent laparoscopic low anterior resections were given IPSS and IIEF questionnaires prior to surgery, and at 1, 3, 6, and 12 months after surgery[22]. The study found patients to have moderate to severe bladder dysfunction in 29.4% of patients at one month which decreased to 2.9% at one year. Of the 17 men who were sexually active prior to surgery, 75% of them reported sexual dysfunction at one month after surgery, which improved with time to 42% of patients at one year after surgery. The sexual dysfunction reported at one year included impotence for 11% of patients, and issues of retrograde ejaculation and decreased climax for 31% patients[22].

There have been multiple randomized trials examining laparoscopic *vs.* open surgery for rectal cancer. The MRC CLASICC trial was a multicenter randomized trial conducted in the UK between 1996 and 2002 in which 794 patients were randomized to either open (n = 268) or laparoscopic (n = 526) surgery for colon or rectal cancer[4,23]. Of these patients, 347 completed questionnaires up to three years post-operatively including the QLQ-C30, QLQ-CR38, IPSS, IIEF, and FSFI. The author found that global quality of life, role functioning, cognitive functioning, pain, and nausea/vomiting remained the same as baseline at 6 months and 3 years after surgery. Social function was worse in the laparoscopic group up to three years after surgery, but remained the same at baseline for the open group. Furthermore, there was no overall difference in bladder function after open *vs.* laparoscopic colorectal cancer surgery. Overall sexual function in men was worse at 3 months after laparoscopic surgery, but by 6 months there was no statistical difference. Additionally, the two independent risk factors for postoperative male dysfunction were TME and conversion to open surgery. Adjusting for neoadjuvant radiation therapy did not change the result as the proportion was similar in both groups. No differences in sexual function were found between laparoscopic *vs.* open surgery for women[4,23]. However, a low response rate from women precluded any meaningful conclusions.

The comparison of open *vs.* laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN) trial in 2014 and colorectal cancer laparoscopic or open resection (COLOR II) trial in 2015 were both multicenter, non-inferiority, randomized controlled trials that concluded that laparoscopic surgery was non-inferior to open surgery for the treatment of rectal cancer in terms of three-year disease free survival, overall survival, and local recurrence[24,25]. In the COREAN trial, the validated Korean version of the EORTC QLQ-CR38 questionnaire was given pre-operatively and at months 3, 12, 24, and 36 months after proctectomy. Clinical meaningful differences in quality of life were considered if a ten point difference in a mean score was identified. No clinically significant differences in quality of life were noted. Therefore, although the study concluded that laparoscopic resection for locally advanced rectal cancer after neoadjuvant chemoradiation was non-inferior to open resection in the context of oncologic outcomes, there was no significant benefit in functional outcomes with laparoscopic surgery compared to open surgery[24]. Quality of life data from the COLOR II trial also demonstrated no difference in sexual dysfunction and micturition symptoms after laparoscopic *vs.* open surgery for rectal cancer[25,26].

While the COREAN and COLOR II trials both concluded in favor of laparoscopic surgery as a safe non-inferior alternative to open surgery, the effect of laparoscopic-assisted resection *vs.* open resection of stage II or III rectal cancer on pathologic outcomes, the ACOSOG Z6051 trial in the U.S. and Australasian laparoscopic cancer of the rectum (ALaCaRT) trial in Australia both found that laparoscopic surgery failed to prove to be non-inferior to open surgery in regards to successful oncologic resections[27,28]. They concluded that the use of laparoscopic surgery for rectal cancer should be conducted with caution. Secondary outcomes including survival and local recurrence are still being collected. Quality of life outcomes will be reported in the future.

A summary of studies examining quality of life after laparoscopic surgery for rectal cancer is found in Table 1.

ROBOTIC SURGERY FOR RECTAL CANCER

Robotic surgery was developed to overcome many of the challenges of laparoscopic surgery while maintaining a minimally invasive approach. The multi-arm robotic platform can provide constant retraction avoiding fatigue, while the steady, high-definition three-dimensional view and enhanced articulation of instruments may allow for a precise dissection. Proponents argue that the approach may decrease the rate of conversion to open surgery, while allowing a more complete TME to achieve a superior oncologic outcome without injury to the sphincters, or nerves involved in urinary and sexual function.

Early studies on robotic surgery for rectal cancer focused on safety and feasibility while more recent studies transitioned to studying oncologic outcomes followed by quality of life measurements. Multiple single center comparison studies have been done reporting both cancer specific outcomes and quality of life assessment. D'Annibale *et al.*[29] in 2013 performed a retrospective study of 60 patients, 30 who underwent robotic TME and 30 who underwent laparoscopic TME, and found that both groups demonstrated significantly worse erectile function one month after surgery. However, erectile function was completely restored one year after surgery in the robotic group but only partially restored in the laparoscopic group. Bladder function was significantly worse at one month after surgery but normalized at one year in both groups[29]. Similarly, a prospective study by Kim *et al.*[30] in 2012 found that out of 30 robotic TME and 39 laparoscopic TME patients, there was an earlier restoration of both bladder function and sexual function in the robotic group compared to the laparoscopic group. This was again demonstrated in another retrospective study of 29 men, 14 who underwent robotic intersphincteric resections, and 15 who underwent laparoscopic intersphincteric resections[31]. The authors found improvement in sexual function at 6 months post-operatively in the robotic group but no difference in bladder function or fecal incontinence[31]. An additional study of robotic *vs*. laparoscopic TME patients demonstrated significant improvement in sexual function in only the robotic group at 6 months[32]. A meta-analysis of these four studies found significant improvement in male sexual function, specifically erectile function at 3 and 6 months after robotic surgery[33]. Although there was a trend toward improved urinary function with robotic surgery compared to laparoscopic surgery, it was not statistically significant[33].

Kamali *et al.*[34] followed 36 consecutive patients, 18 who underwent a laparoscopic anterior resection and 18 who underwent a robotic anterior resection for a median of 12 months after surgery. The EORTC QLQ-CR30 and QLQ-CR29 questionnaires were used. The laparoscopic group reported better social function than the robotic group. The robotic group, however, reported lower pain scales and lower levels of insomnia than the laparoscopic group. Furthermore, there was higher male impotence scores in the laparoscopic group compared to the robotic group (33 ± 35 *vs*. 7 ± 21, $P = 0.03$)[34]. The authors attributed this positive finding to the enhanced vision, sharp targeted dissection, and limited thermal injury of robotic surgery.

Two larger single center studies have been done more recently. One was a quality of life study using a propensity score matched analysis, studying a total of 260 patients (130 robotic and 130 laparoscopic)[35]. Patients were given questionnaires (EORTC QLQ-C30, IPSS, and IIEF-5) preoperatively and at 3, 6, and 12 months after surgery. A subgroup of 48 matched male pairs who were sexually active prior to surgery was analyzed. The matched groups showed no significant differences in quality of life scores prior to surgery. The laparoscopic group had significantly impaired role and social function 3 months after surgery, which the robotic surgery group did not exhibit. At 6 months after surgery, the robotic group had higher emotional function scores than the laparoscopic group. In examining symptom scores, the laparoscopic group showed worsening fatigue, insomnia, and financial difficulties at three months after surgery, which the robotic group did not. The robotic group also had significantly better urinary function (lower IPSS

Table 1. Laparoscopic surgery for rectal cancer

Ref.	Study type	Randomization	Group studied	Sample size	Follow up	Questionnaires	Main findings	Level of evidence
Breukink *et al.*[20], 2007	Prospective single center	No	Lap LAR *vs.* Lap APR	51 (38 Lap LAR, 13 Lap APR)	12 months	SF-36, EORTC QLQ-C30, QLQ-CR38	-LAR had better sexual function, body image, and overall QOL - LAR had less fatigue, pain, appetite loss, and diarrhea at 12 months compared to baseline	2b
Braga *et al.*[21], 2007	Prospective single center	Yes (1:1)	Lap *vs.* Open TME	168 (83 Lap, 85 Open)	12 months	SF-36	-Lap had better overall QOL at 12 months compared to open	1
George *et al.*[22], 2018	Prospective single center	No	Lap TME in male patients	34	12 months	IPSS, IIEF	-Urinary dysfunction in 20% at 3 months to 3% at 9 months - Sexual dysfunction in 75% at 3 months to 42% at 12 months	2b
Jayne *et al.*[4,23], 2007 (CLASICC)	Prospective multicenter	Yes (2:1)	Lap *vs.* Open TME	347 (526 Lap, 268 Open)	36 months	EORTC QLQ-C30, QLQ-CR38	-Lap had worse sexual function at 3 months but no difference at 6 months to 36 months compared to open -Lap had worse social function at 36 months compared to open	1
Jeong *et al.*[24], 2014 (COREAN)	Prospective multicenter	Yes (1:1)	Lap *vs.* Open TME mid to low	340 (170 Lap, 170 Open)	36 months	EORTC QLQ-C30, QLQ-CR38	-No difference in overall QOL at 36 months	1
Andersson *et al.*[25,26], 2014 (COLOR II)	Prospective, multicenter	Yes (2:1)	Lap *vs.* Open TME	385 (260 Lap, 125 Open)	24 months	EORTC QLQ-CR38	-No difference in overall QOL at 24 months	1
Fleshman *et al.*[27], 2015 (ACOSOG Z6051)	Prospective multicenter	Yes (1:1)	Lap *vs.* Open TME	462 (240 Lap, 222 Open)	-	-	-Pending	1
Stevenson *et al.*[28], 2015 (ALaCaRT)	Prospective, multicenter	Yes (1:1)	Lap *vs.* Open TME	475 (238 Lap, 237 Open)	-	-	-Pending	1

Lap: laparoscopic; TME: total mesorectal excision; LAR: low anterior resection; APR: abdominoperineal resection; QOL: quality of life; SF-36: short form general health survey of 36 questions; EORTC QLQ-C30: European organization for research and treatment of cancer quality of life questionnaire, 30 cancer non-specific questions; EORTC QLQ-CR38: European organization for research and treatment of cancer quality of life questionnaire, 38 colorectal cancer specific questions; IPSS: International Prostatic Symptom Score; IIEF: International Index of Erectile Function; Level of evidence: 1: randomized controlled trial; 2a: randomized prospective cohort study; 2b: nonrandomized prospective cohort study; 3: retrospective cohort study; 4: case series

scores) than the laparoscopic group at 6 months in males. Furthermore, the male patients in the robotic group demonstrated a return to baseline in urinary symptoms at 12 months that was not achieved in the laparoscopic group. There were no significant differences found in female patients between groups compared to baseline. Sexual function returned to baseline at 6 months in the robotic group, but did not return to baseline until 12 months after surgery in the laparoscopic group. Overall, this study showed that although quality of life worsens initially after surgery, the robotic group had an earlier return to baseline quality of life than the laparoscopic group[35].

Another large single center study compared open (n = 114) *vs.* robot-assisted (n = 108) intersphincteric resections and found that at 6 and 12 months post operatively, robotic-assisted surgeries resulted in improved fecal incontinence scores (12.5 and 7.7 in the robotic group, and 14.2 and 10.3 in the open group, $P < 0.001$)[36]. At 6 months post-operatively, severe sexual dysfunction occurred 2.7 times more in the open group than the robotic-assisted group (34.1% *vs.* 12.5%; $P = 0.023$) in male patients over the age of 65. Specifically, erectile dysfunction was more common in the open group than the robotic group (31.8% *vs.* 12.5%, $P = 0.04$)[36].

There is only one randomized study looking at quality of life between the robotic and laparoscopic approach. Jayne *et al*.[37] conducted the effect of robotic *vs*. laparoscopic resection for rectal cancer (ROLARR) trial. In this international multicenter study, 471 patients were randomized between 2011 and 2014 to either robotic-assisted or laparoscopic rectal cancer surgery for either high (upper rectum) or low (total rectum) anterior resection or abdominoperineal resection (rectum and perineum). The study included 40 surgeons at 29 sites across 10 countries between 2011 to 2014. To be part of the study, surgeons were required to have performed 30 minimally-invasive rectal resections with at least 10 robotically and 10 laparoscopically. On average, patients received an operation performed by a surgeon with experience of a median 91 previous laparoscopic operations or a median 50 previous robotic-assisted operations. The primary outcome revealed a conversion to open rate of 8.1% for robotic-assisted and 12.2 % for laparoscopic surgery with no statistical significant difference (P = 0.16). The two factors that did show a statistically significant odds ratio for conversion to open surgery were a high body mass index and male gender. Of the two quality of life measures compared, bladder dysfunction and sexual dysfunction, neither were statistically different. The IPSS scores for bladder function were similar at baseline between the two groups pre-operatively and at 6 months post-operatively. In examining male sexual dysfunction with IIEF scores and female sexual dysfunction with FSFI scores, no statistically significant differences were identified between groups comparing baseline scores to 6 months after surgery[37].

A summary of studies examining quality of life after robotic surgery for rectal cancer is found in Table 2.

TEM

TEM is a method by which select mid and proximal T1N0 rectal cancer and adenomas are excised endoscopically. A 40 mm diameter and up to 20 cm long rectoscope is inserted through the anus using a blunt obturator. Once the obturator is removed, a faceplate with ports is inserted. An insufflation system generates and maintains constant pneumorectum. The entire rigid platform is attached to the operating table. Proponents describe the technique as one allowing a local excision to be performed with a lower rate of positive margins, tumor fragmentation, and local recurrence compared to transanal excision[38]. Furthermore, the technique allows for the local resection of more proximal tumors than accessible through conventional transanal excision to be performed without a transabdominal complete mesorectal excision and rectal resection. This technique additionally negates the need for a diverting stoma. However, critics argue that the 40 mm diameter rectoscope may stretch the sphincter complex, impair anorectal function, and can cause fecal incontinence impairing quality of life. Furthermore, the cost of the instruments and platforms is greater than that of a TAMIS set up, but less than open surgery.

Allaix *et al*.[39] was one of the first to assess TEM for effects on quality of life. They studied 93 patients who had undergone TEM for benign rectal lesions or T1N0 rectal cancer and found that the Wexner incontinence scale (range 0-10) was increased from baseline at 3 months, began to decline at 12 months and returned to baseline preoperative value at 60 months[39]. Another single center study was conducted in which a EuroQol (EQ-5D-5L) quality of life questionnaire and a Wexner fecal incontinence scale was given to 132 patients who underwent TEM for a variety of rectal lesions including adenocarcinoma with a median follow-up period of 96 months[40]. Those considered to have minor to no fecal incontinence were rated as having a Wexner score of 2 or less. Those considered to have non-minor incontinence were rated as having a Wexner score of 3 or more. Thirty eight patients (28.8%) had higher Wexner scores of 3 or more and worse quality of life. The study concluded that TEM has significant rate of fecal incontinence that impairs quality of life. In comparison to laparoscopic low anterior resections which have reported Wexner scores of 5.2 ± 4.2 at 6 months postoperatively, and scores of 3.7 ± 3.4 at 12 months, the Wexner scores were similar for TEM[40]. TEM, however, still results in much lower fecal incontinence than open surgery which has reported Wexner scores as high as 14.2 at 6 months and 10.3 at 12 months after surgery[36].

Another single center study followed 102 patients after TEM, including benign and malignant lesions, from 2009 to 2012[41]. Questionnaires including the European quality of life 5 dimensions questionnaire (EQ-

Table 2. Robotic surgery for rectal cancer

Ref.	Study type	Randomization	Group studied	Sample size	Follow up	Questionnaires	Main findings	Level of evidence
D'Annibale *et al.*[29], 2013	Retrospective single center	No	Robot *vs.* Lap TME	60 men (30 Robot, 30 Lap)	12 months	IPSS, IIEF	-Both robot and lap had decreased urinary function at 1 month and was restored by 12 months -Robot had better sexual function at 12 months compared to lap	3
Kim *et al.*[30], 2012	Prospective single center	No	Robot *vs.* Lap TME	69 (30 Robot, 39 Lap)	12 months	IPSS, IIEF	-Robot recovered urinary function at 3 months compared to 6 months in lap -Robot recovered sexual function at 6 months compared to 12 months in lap	2b
Park *et al.*[31], 2013	Retrospective single center	No	Robot *vs.* Lap TME (with ISR)	29 men (14 Robot, 15 Lap)	6 months	Wexner, IPSS, IIEF	-Robot had better sexual function at 6 months compared to lap -No difference in fecal incontinence and urinary function	3
Park *et al.*[32], 2014	Retrospective single center (case matched)	No	Robot *vs.* Lap TME	64 (32 Robot, 32 Lap)	12 months	IPSS, IIEF	-Robot had better sexual function at 6 months but both equal at 12 months compared to lap -No difference in urinary function	3
Kamali *et al.*[34], 2017	Prospective single center	No	Robot *vs.* Lap TME	36 (18 Robot, 18 Lap)	12 months	EORTC QLQ-CR30, QLQ-CR29	-No difference in global health -Robot had better social function, insomnia scores, pain scores compared to lap -Robot had better impotence scores compared to lap	2b
Kim *et al.*[36], 2014	Retrospective single center	No	Robot *vs.* Open TME with ISR	222 (108 Robot, 114 Open)	12 months	FISI, Lawson, VAS	-Robot had better fecal incontinence scores compared to open -Robot had better sexual function compared to open	3
Kim *et al.*[35], 2018	Prospective single center	No	Robotic *vs.* Lap TME	260 (130 Robot, 130 Lap)	12 months	EORTC QLQ-C30, IPSS, IIEF	-Robot had better emotional and social function compared to lap -Robot had better symptoms of fatigue, insomnia, and financial issues compared to lap -Robot had better sexual function compared to lap -Robot had earlier return of social function compared to lap	2b
Jayne *et al.*[37], 2017	Prospective multicenter	Yes	Robot *vs.* Lap TME	471 (237 Rob, 234 Lap)	6 months	IPSS, IIEF, FSFI	-No difference in overall QOL at 6 months	1

Lap: laparoscopic; TME: total mesorectal excision; ISR: intersphincteric resection; QOL: quality of life; SF-36: short form general health survey of 36 questions, EORTC QLQ-C30: European organization for research and treatment of cancer quality of life questionnaire, 30 cancer non-specific questions; EORTC QLQ-CR38: European organization for research and treatment of cancer quality of life questionnaire, 38 colorectal cancer specific questions; IPSS: International Prostatic Symptom Score; IIEF: International Index of Erectile Function; FSFI: Female Sexual Function Index; ICIQ-MLUTS: International consultation on incontinence male lower urinary tract symptoms; ICIQ-FLUTS: International consultation on incontinence female lower urinary tract symptoms; FISI: Fecal Incontinence Severity Index; VAS: visual analogue scale; Wexner: Wexner Fecal Incontinence Score; Level of evidence: 1: randomized controlled trial; 2a: randomized prospective cohort study; 2b: nonrandomized prospective cohort study; 3: retrospective cohort study; 4: case series

5D), EORTC QLQ-C30, and QLQ-CR29 were completed by patients pre-operatively and at 6, 12, 26, and 52 weeks after surgery. Quality of life diminished at 6 and 12 weeks after TEM compared to baseline ($P < 0.05$), but returned to baseline by 26 weeks. Anorectal function was worse at 6 weeks after surgery but returned to preoperative function at 12 weeks. Urinary function was not affected at any point after surgery. The study concluded that TEM has a transient and reversible impact on quality of life and anorectal function, without affecting urinary function[41].

TEM has also been studied as a treatment after neoadjuvant chemotherapy and radiation. In a study comparison between 31 patients with T2 and T3 rectal cancer who underwent either TEM *vs.* laparoscopic TME after neoadjuvant therapy, the authors found that the TEM resulted in better body image ($P = 0.006$), defecation function ($P = 0.01$) and weight loss ($P = 0.005$) than the laparoscopic group[42]. At one month after surgery, the TEM group had better symptoms in terms of nausea, vomiting, appetite loss, and constipation compared to the laparoscopic group. At 6 months, the laparoscopic group had significantly worse global health status, emotional function, insomnia, and appetite loss, body image, and defecation problems. At one year, the TEM group showed better body image, defecation problems and weight loss compared to the laparoscopic group[42].

A summary of studies examining quality of life after TEM for rectal cancer is found in Table 3.

TAMIS

TAMIS emerged recently as an alternative to TEM. A flexible transanal multichannel laparoscopic port is used that is shorter in length than the conventional TEM rectoscope. Advocates state the benefit of TAMIS as being easier to learn for surgeons who are already proficient in laparoscopy, and more readily available because no specialized insufflators are needed. Furthermore, the flexible TAMIS platform is lower in cost and requires less time to setup than TEM. Contrary to TEM which uses a long rectoscope and insufflation, the TAMIS technique depends entirely on adequate insufflation for maximal exposure due to the short length of the port. Similar to TEM, TAMIS does not include a TME, and therefore usually yields no nodal information. Existing data suggests that TAMIS and TEM both only be performed for rectal adenomas and low risk T1N0 rectal cancers, and patients who refuse proctectomy. If final pathology does reveal high risk features, positive margins, high tumor grade, then a salvage TME or adjuvant therapy may be needed.

In 2016, a short-term single-center study followed 24 patients with rectal adenomas and low risk T1 cancers with a median tumor height of 8 cm from the anal verge from 2011 to 2013 before TAMIS and 6 months afterwards (2-17 cm)[43]. In total, there were 20 adenomas and 4 low risk T1 cancers. Functional outcomes were assessed with the fecal incontinence severity index (FISI), and fecal incontinence quality of life (FIQL), and the generic EuroQol EQ-5D questionnaire. FISI and FIQL scores were unchanged from baseline at 6 months, and EQ-5D improved at 6 months[43]. García-Flórez *et al.*[44] followed 32 patients who underwent TAMIS over a 40 months period. These patients were not given quality of life questionnaires but questioned during clinic visit. Four weeks after surgery, 5 patients (15%) complained of minor fecal incontinence to flatus or liquid stool. However, by eight weeks after surgery the incontinence resolved. No urinary or sexual dysfunction was affected. This study revealed that TAMIS resulted in good short-term and long-term functional outcomes comparable to TEM[44].

Another study published in 2018 compared 37 patients who underwent a TAMIS between 2011 and 2014, and then compared their quality of life outcomes to 37 matched healthy controls to the same age, gender, and socio-economic status[45]. Questionnaires including the SF-36 and FISI questionnaire were given after a median follow-up duration of 36 months to patients with either adenomas or T1 carcinomas. They found that TAMIS resulted in impaired social function. This worsening was attributed possibly to the fecal incontinence that occurred in 70% of the patients who underwent TAMIS. The FISI score worsened from 8.3 points pre-operatively to 10.1 points 3 years after this study. TAMIS patients reported an overall similar quality of life in comparison to their counterparts. TAMIS patients scored a higher mental health and bodily pain

Table 3. Transanal endoscopic microsurgery

Ref.	Study type	Randomization	Group studied	Sample size	Follow up	Questionnaires	Main findings	Level of evidence
Allaix *et al*.[39], 2011	Prospective single center	No	TEM	93	60 months	Wexner, FIQL, EORTC QLQ-C30, QLQ-CR38, EQ5D	-TEM had mild fecal incontinence postop which returned to baseline by 60 months -Study group had benign and malignant lesions	4
Jakubauskas *et al*.[40], 2018	Prospective single center	No	TEM	132	96 months	Wexner, EQ5D	-TEM had similar fecal incontinence scores compared to historic lap scores, but better than open surgery -Study group had benign and malignant lesions	4
Hompes *et al*.[41], 2015	Prospective single center	No	TEM	102	12 months	EORTC QLQ-C30, QLQ-CR29, EQ5D	-TEM had mild fecal incontinence postop which returned to baseline by 26 weeks -TEM had overall QOL effects which were transient -TEM had no effect on urinary function -Study group had benign and malignant lesions	4
D'Ambrosio *et al*.[42], 2016	Prospective single center	No	Neoadjuvant TEM *vs*. Lap TME	31 (15 TEM, 16 lap TME)	12 months	EORTC QLQ-C30, QLQ-CR38	-TEM had improved overall QOL at 1, 6, 12 months than lap TME	2b

TEM: transanal endoscopic microsurgery; Lap: laparoscopic; TME: total mesorectal excision; QOL: quality of life; EORTC QLQ-C30: European organization for research and treatment of cancer quality of life questionnaire, 30 cancer non-specific questions; EORTC QLQ-CR38: European organization for research and treatment of cancer quality of life questionnaire, 38 colorectal cancer specific questions; EORTC QLQ-CR29: European organization for research and treatment of cancer quality of life questionnaire, 29 colorectal cancer specific questions; FIQL: Fecal Incontinence Quality of Life Scale; EQ5D: European quality of life 5 dimensions questionnaire; Wexner: Wexner Fecal Incontinence Score; Level of evidence: 1: randomized controlled trial; 2a: randomized prospective cohort study; 2b: nonrandomized prospective cohort study; 3: retrospective cohort study; 4: case series

score compared to the control group. The authors described this as a "rejoice phenomenon" when the patient describes improved mental health after surgery with relief that a malignancy has been successfully excised. The study therefore concluded that TAMIS patients have similar quality of life compared to healthy controls, and social function is decreased which may or may not be related to fecal incontinence[45].

A summary of studies examining quality of life after TAMIS for rectal cancer is found in Table 4.

TaTME

TaTME is an emerging technique for the treatment of mid and low rectal cancer referred to as a "bottom-up" approach or transanal proctectomy described by Sylla *et al*.[46] in 2010. Advocates attribute the benefits of the technique to decrease the "coning in" effect of conventional TMEs that may result in an incomplete distal mesorectal excision. Additionally, the technique is purported to allow for accurate identification of the distal resection margins, increased rate of sphincter preservation, and reduced sexual and urinary dysfunction. It is believed to be most beneficial for patients with narrow pelvises and excessive visceral fat. Others believe the technique results in lower conversion rates and reduced wound-related complications. However, major concerns about the technique include having a low tenuous anastomosis closer to the anal sphincter compared to laparoscopic or robotic TME, as well as anal sphincter damage caused by prolonged

Table 4. Transanal minimally invasive surgery

Ref.	Study type	Randomization	Group studied	Sample size	Follow up	Questionnaires	Main findings	Level of evidence
Verseveld *et al*.[43], 2016	Prospective single center	No	TAMIS	24	6 months	FISI, FIQL, EQ5D	-TAMIS had no change in fecal incontinence compared to baseline -TAMIS had better overall QOL improved compared to baseline -Study group had benign and malignant lesions	4
García-Flórez *et al*.[44], 2017	Retrospective single center	No	TAMIS	32	40 months	Questions at clinic visit	-TAMIS had fecal incontinence postop that resolved -TAMIS had no change in urinary or sexual function -Study group had benign and malignant lesions	3
Clermonts *et al*.[45], 2018	Prospective single center (Case matched)	No	TAMIS *vs*. healthy controls	37 (37 TAMIS, 37 healthy controls)	36 months	SF-36, FISI	-TAMIS had similar overall QOL compared to healthy patients -TAMIS had worse social function compared to healthy patients -TAMIS had better bodily pain scores compared to open -Study group had benign and malignant lesions	3

TAMIS: transanal minimally invasive surgery; QOL: quality of life; SF-36: short form general health survey of 36 questions; EQ5D: european quality of life 5 dimensions questionnaire; FISI: Fecal Incontinence Severity Index; FIQL: Fecal Incontinence Quality of Life Scale; Level of evidence: 1: randomized controlled trial; 2a: randomized prospective cohort study; 2b: nonrandomized prospective cohort study; 3: retrospective cohort study; 4: case series

dilation of the anal canal. Furthermore, given the learning curve required for the technique, there may be increased risk of adjacent structures such as the pelvic floor muscles, prostatic urethra, and neurovasculature[47]. Most early single center short term studies described TaTME with similar outcomes in terms of operation time, blood loss, length of stay, and complication rates compared to laparoscopic TME[48]. Chang and Kiu[49] performed a single center study in 2018 that found in comparing transanal TME *vs*. laparoscopic surgery, that there were no significant differences in 30 day complication rate or pathologic outcomes. Atallah *et al*.[50] described the results of a structured training program to teach TaTME, and found that surgeons early in their experience may have complications such as urethral injury (5/20; 25%) and significant hemorrhage (3/20, 15%). Maykel described a comprehensive TaTME training program and described their experience with 40 patients and demonstrated the ability to achieve 100% complete mesorectal excision, acceptable leak rate of 6.5%, low wound infection risk of 10%, and a overall complication rate of 32.6% comprised of minor complications such as ileus 7.9%, urinary retention 7.9%, and urinary tract infections 5%[51,52]. There were no urethral or ureter injuries in their group[51,52].

In 2017, Koedam *et al*.[53] published a single center study examining the quality of life impact of TaTME in 30 rectal cancer patients who all underwent restorative coloanal anastomoses. Seventy-three percent of these patients underwent neoadjuvant therapy with either radiation only (40%) or chemoradiation (33%). These patients were evaluated prospectively, and given four questionnaires and found that the overall quality of life was significantly decreased at one month, but returned to near preoperative score at 6 months. This study found similar responses regarding the cancer-specific and colorectal cancer-specific questionnaires, in which scores dropped significantly one month after surgery, but were no longer significantly different at 6 months after surgery except for social function (P = 0.013) and anal pain (P = 0.013). Bladder function, male sexual function, and anorectal function after stoma closure was similarly significantly worse at one month postoperatively but not significantly different after 6 months[53].

Another recent study examined 54 consecutive patients with rectal cancer (27 had TaTME *vs.* 27 had laparoscopic TME) and found that there were comparable functional and quality of life outcomes at 6 months. On the EORTC QLQ-CR29 questionnaire, more patients in the TaTME group reported more fecal incontinence *vs.* the laparoscopic TME group, but the overall low anterior resection syndrome (LARS) score was no different[54].

Two ongoing multicenter trials will examine quality of life outcomes in patients who undergo transanal TME. The COLOR III trial will be an international multicenter superiority trial that will compare 1098 patients with mid or low rectal cancers scheduled for either transanal TME and conventional laparoscopic TME for the treatment of low rectal cancers[55]. Although the primary endpoint will be the circumferential resection margin, the secondary endpoints will include disease-free survival, overall survival, and quality of life. Serra-Aracil *et al.*[56] published a protocol to study a combined TaTME combined with laparoscopy to evaluate if there would be a lower conversion rate than laparoscopic low anterior resection, and potentially improve patient recovery and overall morbidity, and quality of life measures. Quality of life measures will be examined preoperatively and 6 months after the closure of protective ileostomy using the EORTC QLQ-C30, QLQ-CR29, and LARS score.

A summary of studies examining quality of life after TaTME for rectal cancer is found in Table 5.

DISCUSSION

The ideal treatment objectives for rectal cancer include local and systemic disease control, overall survival and preservation of quality of life. Oncologic outcomes can be measured objectively, following rates of recurrence and mortality in follow up. On the other hand, questionnaires remain the mainstay of collecting data on quality of life in rectal cancer patients. These instruments are cost-efficient and practical, and tremendous amounts of data points can be collected in one setting. However, disadvantages of questionnaires include possible low completion rate, subjective nature of responses, issues interpreting the questions, lack of conscientious responses, and inability to probe responses. In addition, there may be a statistically significant numeric difference found on a quality of life instrument between two approaches, but may not be clinically relevant. Moreover, the term "quality of life" encompasses many facets of a patient's well-being and includes not only fecal incontinence, urinary incontinence, and sexual function, but also body image, pain, social connections and participation in activities of daily living. As a result, there are many types of questionnaires and not all studies utilize the same surveys. These factors make it challenging at times to compare quality of life data across studies. Large randomized studies should all utilize the most validated and updated scales available.

The results of our review suggest that minimally invasive surgeries for rectal cancer have tremendous potential in achieving equivalent outcomes to conventional open surgeries with the possible benefit of an improved quality of life. Most early studies of each of these MIS techniques were single institution and observational, focusing on safety and feasibility, and then cancer-specific outcomes. As experience grew, there was a transition to comparative studies, and then finally randomized control trials. Later studies examine quality of life as a relevant outcome. The most frequently used quality of life questionnaires were EORTC QLQ-C30, the colorectal module QLQ-CR38 and the SF-36, all validated instruments. Early single center studies of laparoscopic TME showed potential benefit in quality of life with an MIS approach[20-22].

Table 5. Transanal total mesorectal excision

Ref.	Study type	Randomization	Group studied	Sample size	Follow up	Questionnaires	Main findings	Level of evidence
Koedam *et al.*[53], 2017	Prospective single center	No	TaTME	30	6 months	EORTC QLQ-C30, QLQ-CR29, EQ5D, LARS	-TaTME had decreased urinary function, sexual function, fecal incontinence and overall QOL at 1 month compared to baseline and returned to normal by 6 months -TaTME had decreased social function and anal pain at 6 months compared to baseline -TaTME had major LARS in 33% after ileostomy closure	4
Veltcamp Helbach *et al.*[54], 2018	Prospective single center	No	TaTME *vs.* Lap TME	54	6 months	EORTC QLQ-C30, QLQ-CR29, EQ5D, LARS, IPSS	-TaTME had similar QOL compared to lap -TaTME had worse fecal incontinence compared to lap (EORTC QLQ-CR29 only)	2b
Deijen *et al.*[55], 2016 (COLOR III)	Prospective multicenter	Yes (2:1)	TaTME *vs.* Lap TME	1098	60 months	EORTC QLQ-C30, QLQ-CR29, EQ5D, LARS	-Pending	1
Serra-Aracil *et al.*[56], 2018	Prospective multicenter	Yes (1:1)	TaTME *vs.* Lap TME	116	6 months	EORTC QLQ-C30, QLQ-CR29, LARS	-Pending	1

TaTME: transanal total mesorectal excision; Lap: laparoscopic; TME: total mesorectal excision; LARS: low anterior resection syndrome; QOL: quality of life; EORTC QLQ-C30: European organization for research and treatment of cancer quality of life questionnaire, 30 cancer non-specific questions; EORTC QLQ-CR29: European organization for research and treatment of cancer quality of life questionnaire, 29 colorectal cancer specific questions; EQ5D: European quality of life 5 dimensions questionnaire; IPSS: International Prostatic Symptom Score; Level of evidence: 1: randomized controlled trial; 2a: randomized prospective cohort study; 2b: nonrandomized prospective cohort study; 3: retrospective cohort study; 4: case series

However, in contrast, the recent multicenter randomized controlled trials have shown the results to be either equivalent or worse in the laparoscopic group[23-26]. It will be important to follow the final long term quality of life findings of the large randomized control trials of ACCOSOG Z6051 and ALaCaRT[27,28]. This may underscore the inherent problem of working in the fixed space of the bony pelvis with conventional laparoscopy. Restricted movements of working instruments, two-dimensional view, difficult ergonomics and an unstable platform can make laparoscopy for rectal cancer challenging and may lead to a high conversion rate or unsatisfactory dissection.

Key advances in robotic technology over the last two decades overcame challenges of laparoscopic and open surgery and allowed for enhanced three-dimensional view, and "wristed" instruments allowing for multiple degrees of freedom, a stable platform, and improved ergonomics. This was particularly important in complex colon and rectal surgery including procedures in the bony pelvis. For these reasons, robotic usage for all colorectal procedures grew from 2.6% to 6.6% between 2011-2015. In 2015, robotic utilization for rectopexy was 27%, for low anterior resection was 13%, and for abdominoperineal resection was 15%[57]. Although the technology has been limited by decreased haptics, steep learning curve, and concern of increased cost, widespread utilization of robotics is spreading quickly. In terms of quality of life, robotic surgery may be more promising than laparoscopic surgery in its improvement in chronic pain and insomnia based on single center studies, showing an earlier return to baseline quality of life compared to laparoscopic surgery. Furthermore, several small single center short term studies demonstrated a significant improvement in sexual function. One study even showed a modest improvement in bladder function in robotic surgery patients compared to laparoscopic surgery patients[29-36]. Benefits have been attributed to the superior dissection allowed by robotic surgery. However, the multicenter ROLARR study showed that at 6 months there was no benefit in robotic surgery in terms of quality of life outcomes[37]. The three year results have yet to be reported. Like laparoscopic surgery though, robotic surgery may prove to have better outcomes in future trials once participating surgeons gain more expertise on their learning curve. The surgeons in the ROLARR trial had varying levels of experience: surgeons performing laparoscopy had an average of 91 previous laparoscopic cases while surgeons performing a robotic approach had an average of 50 previous robotic cases, possibly still in their learning curve. In addition, robotic systems are still in their infancy with newer robotic platforms and technology becoming more widely available.

TEM and TAMIS both allow for local resections that do improve quality of life compared to transabdominal surgeries that require rectal resections and increase need for diverting or permanent ostomies. These procedures require stretching of the anorectal ring, and patients should be counseled that may have some transient changes to their bowel function that can last several months. These modalities are mostly limited to treatment of early stage cancers. TEM and TAMIS may have a role for local excision after neoadjvuant therapy as well. This will need to be studied more closely with overall effect on quality of life in future randomized studies.

Transanal TME is the newest of MIS rectal cancer treatments and only small retrospective studies have described its effects on quality of life[53,54]. There has been some early concern for effect on incontinence and LARS scores possibility due to the low anastomosis. Morbidity including urethral injury warrants the need of continued studies as surgeons gain more experience. TaTME should be limited to surgeons who have taken the proper courses and have adequate mentoring. Studies comparing transanal TME to other approaches of rectal cancer treatment need to be conducted to better assess the potential benefit in cancer-specific outcomes and patients' overall wellbeing. Two future randomized studies may help clarify these questions[55,56].

In addition to the aforementioned MIS approaches, a new treatment strategy for rectal cancer has the potential to change quality of life after therapy for rectal cancer. This "watch-and-wait" strategy is for select patients who demonstrate a complete clinical response to total neoadjuvant therapy. These patients are observed closely and do not undergo any proctectomy or local excision if they show no evidence of recurrence in follow-up. This option is being extensively studied and can be used in multiple scenarios including after treatment for locally advanced (any T3, or N+) and for lower risk tumors including T2 and high risk T1 lesions[58]. A small study of 29 near-complete responders who underwent TEM *vs.* 53 complete responders to neoadjuvant chemotherapy who underwent no further surgery demonstrated a statistically significant improvement in quality of life and incontinence scores in those patients that had a complete response (and no TEM) at the end of a three year follow-up period (2.3 *vs.* 6.5, $P < 0.001$)[59]. In another study comparing 41 watch-and-wait patients to 41 patients who had neoadjuvant and surgery matched by gender, age, tumor stage, and tumor height, two year follow-up revealed better physical and cognitive function, body image, and overall global health status in the watch-and-wait group compared to the surgical group. Furthermore, the "watch-and-wait" patients had fewer problems with defecation, sexual and urinary tract function[60]. The quality of life problems that are noted in the "watch-and-wait" group can be partly attributed to the effects of radiation therapy alone and its known effects on fecal incontinence and genitourinary function. Still, "watch-and-wait" treatment may be a valid option for complete clinical responders in the future. More studies will need to be done evaluating the concordance of complete clinical response with a true pathologic complete response to limit future recurrence. "Watch-and-wait" has the potential to profoundly impact quality of life after therapy for rectal cancer.

Surgery for rectal cancer is difficult and continues to evolve. Completing a TME safely relies on multiple patient and surgeon factors. Any approach, including organ-preserving options and local excision, can be associated with significant changes in quality of life. Care must be taken to study innovative new treatment algorithms and technical advances with assessment of both oncologic and functional outcomes. An ideal trial looking at quality of life would be a large randomized controlled trial with adequate power, baseline and long term quality of life assessment with a high response rate using the most commonly-used and validated questionnaires.

CONCLUSION

MIS in the treatment of rectal cancer is ever evolving, with a continuous effort to achieve equivalent if not better oncologic outcomes with less surgical trauma and maintain, and possibly improve functional outcomes. Surgeons continue to use new tools and approaches to maximize patient benefit. Future studies should include surgeons with proficient experience in new minimally invasive robotic and transanal rectal cancer surgery, all in an effort to help patients live longer and live better.

DECLARATIONS

Authors' contributions

Conception and design of the work, acquisition, analysis, interpretation of data, drafting and revising the work: Chen JH, Bello BL

Conception and design of the work, revising the work: Ayscue JM, Bayasi M, Fitzgerald JF, Stahl TJ

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Mini-invasive Surgery

Original Article

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Robotic-assisted total mesorectal excision in low-lying rectal cancer

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Abstract

Aim: To evaluate the feasibility, safety, and short-term oncological outcomes of robotic-assisted total mesorectal excision (TME) in patients with low-lying rectal cancer (≤ 5 cm from anal verge).

Methods: We enrolled 60 patients with stages I-III low-lying rectal cancer who underwent robotic-assisted TME at a single institution between July 2013 and April 2017.

Results: Of the 60 patients enrolled, 49 (81.6%) underwent preoperative concurrent chemoradiotherapy. Furthermore, among these 49 patients, 18 (36.7%) achieved a pathologic complete response. R0 resection was performed in 57

(95%) patients. Circumferential and distal resection margins were positive in 3 (5%) and 1 (1.6%) patients, respectively. The sphincter preservation rate was 93.3% (56/60). The overall complication rate was 21.7% (13/60), with an anastomotic leakage rate of 3.3% (2/60); most of these instances were mild and the patient recovered uneventfully.

Conclusion: The results demonstrate that robotic-assisted TME is safe and feasible for patients with low-lying rectal cancer.

Keywords: Robotic-assisted total mesorectal excision, low-lying rectal cancer, R0 resection, circumferential resection margin

INTRODUCTION

In 2014, approximately 15,000 new cases of colorectal cancer were diagnosed in Taiwan, and in approximately 5,600 of cases, the patient died. Total mesolectal excision (TME) surgery, reported by Heald *et al.*[1] in 1982, has resulted in decreased 5-year local and overall recurrence rates. MacFarlane *et al.*[2] reported the importance of identifying the "holy plane", that is, the surgeon's dissection that will encompass the malignancy and yet preserve autonomic neural function. Radiation therapy offers noteworthy benefits to many patients with rectal cancer; preoperative radiation is superior to postoperative radiation. Preoperative radiation combined with chemotherapy (chemoradiotherapy) is used for locally advanced rectal cancer. A German study suggested that compared with postoperative chemoradiotherapy, preoperative chemoradiotherapy improved local control and was associated with reduced toxicity, but did not improve overall survival[3,4]. We achieved similar results from other studies[5-7].

Laparoscopic rectal surgery was as safe as open surgery and resulted in improved recovery rates[8,9]. However, the robotic system has several advantages over laparoscopic surgery, such as a high-definition three-dimensional vision, smooth movement of instruments, and absence of surgeon tremor. Thus, this robotic system can be anticipated to assist with dissections in the narrow pelvic cavity. Since the first robotic colon surgery in 2002[10], it is believed to have the potential to improve compliance with minimal invasive surgery. For rectal cancers, robotic surgery has been demonstrated to be as safe and feasible as laparoscopic and open surgical procedures[11-14].

The unique anatomy of the rectum, with its retroperitoneal location in the narrow pelvis, makes surgical access relatively difficult. The visceral endopelvic fascia, also known as fascia propria, is identified by a loose areolar tissue that circumferentially separates the rectum and mesorectum from surrounding pelvic structures. Removal of the rectum with the mesoretum intact ensures the complete removal of all lymph nodes and lymphatics from the diseased rectum and thus prevents oncologic contamination of the pelvis during surgery. In this study, we present the short-term oncological outcomes of patients with low-lying rectal cancer who underwent complete robotic-assisted TME.

METHODS

Patients

The data included 60 patients with low-lying rectal cancer (adenocarcinoma) stages I-III who underwent complete robotic-assisted TME with the da Vinci® surgical system at a single institution between July 2013 and April 2017. The study was approved by the institutional review board of our hospital. Informed consent was obtained from each patient before performing the robotic surgery. All patients underwent routine preoperative colonoscopy and abdominal and pelvic computed tomography (CT) or magnetic resonance imaging for preoperative staging. Low-lying rectal cancer was defined as a tumor located at or less than 5 cm from the anal verge. Patients with T3, T4, or N+ rectal cancer received preoperative concurrent chemoradiotherapy (CCRT). Furthermore, a 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen or a fluoropyrimidine-based regimen was prescribed. Long-course radiotherapy (total of 5000 cGy in 25 fractions) was concurrently administered. The median time interval between radiotherapy completion and robotic surgery was 91 (range, 47-363) days.

We thoroughly evaluated the surgical outcomes, including the operation time (with operation, console, and docking times), blood loss, complication rates, and pathologic clearance, including the positive circumferential resection margin (CRM) and distal resection margin (DRM) rates. Docking time was defined as the time taken to position the robot and mount the robotic arms. Postoperative follow-up studies included physical examination and serum CEA assay every 3 months for the first 2 years and thereafter every 6 months. Chest radiograph was taken every 6 months and abdominopelvic CT was taken annually in the following years. Colonoscopy was performed annually.

Surgical procedure

The single-docking technique with five or six ports was used as the docking method[15]. The da Vinci® Si Surgical System was docked over the left flank of the patient. The second arm was engaged at the right upper trocar, and the first and third arms worked at the left medial and lateral trocars, respectively [Figure 1A and B]. An assistant on the right side of the patient used one or two ports for suctioning and additional retraction. High dissection and low ligation of the inferior mesenteric vessel and mobilization of the left colon was done but splenic flexure was not taken down regularly[16]. The inferior mesenteric vein was also identified but was not ligated immediately. The intraoperative view of robotic-assisted total mesorectal excision compared with laparoscopic total mesorectal excision showed more clear obviously [Figure 1C and D]. Complete robotic-assisted TME with single-docking technique was performed in all patients.

After complete mobilization of the sigmoid or descending colon, mesocolon, and entire rectum after TME, low anterior resection (LAR) with the double-staple technique, intersphincteric resection (ISR) with coloanal anastomosis [Figure 1E and F] and loop colostomy, or abdominoperineal resection was accordingly performed[16]. For the ISR of the perineal part, we used the Lone Star Retractor System® to assist operation. The specimen was then extracted and resected transanally (natural orifice specimen extraction, Figure 1G). Coloanal anastomosis was performed using the hand-sewn method. A loop colostomy of the transverse colon was created. A drain tube was placed into the pelvic cavity through laparoscopic assistance.

Statistical analysis

All data were statistically analyzed using SPSS Version 19.0 (SPSS Inc., Chicago, IL, USA). All patients were followed up until their death, last follow-up, or 30 April 2017. The operation time was defined as the time between the initial skin incision and wound closure completion. A P value of < 0.05 denoted statistical significance. Overall survival was defined as the time from surgery to death or to the last date the patient was known to be alive. Disease-free survival was defined as the time from surgery to recurrence of cancer or to the last date the patient was known to be disease free. Overall survival and disease-free survival were obtained using the Kaplan-Meier method.

RESULTS

Patients' characteristics and perioperative outcomes

Of the enrolled patients, 36 were men and 24 were women. The median age was 62 years (range, 24-92). Forty-nine (81.7%) patients had neoadjuvant chemoradiotherapy. The details of patient characteristics are presented in Table 1.

The most frequent surgical procedure performed was ISR (37/60, 61.7%). ISR with coloanal anastomosis was performed in 37 patients, and abdominoperineal resection was performed in 4 patients. Protective di-

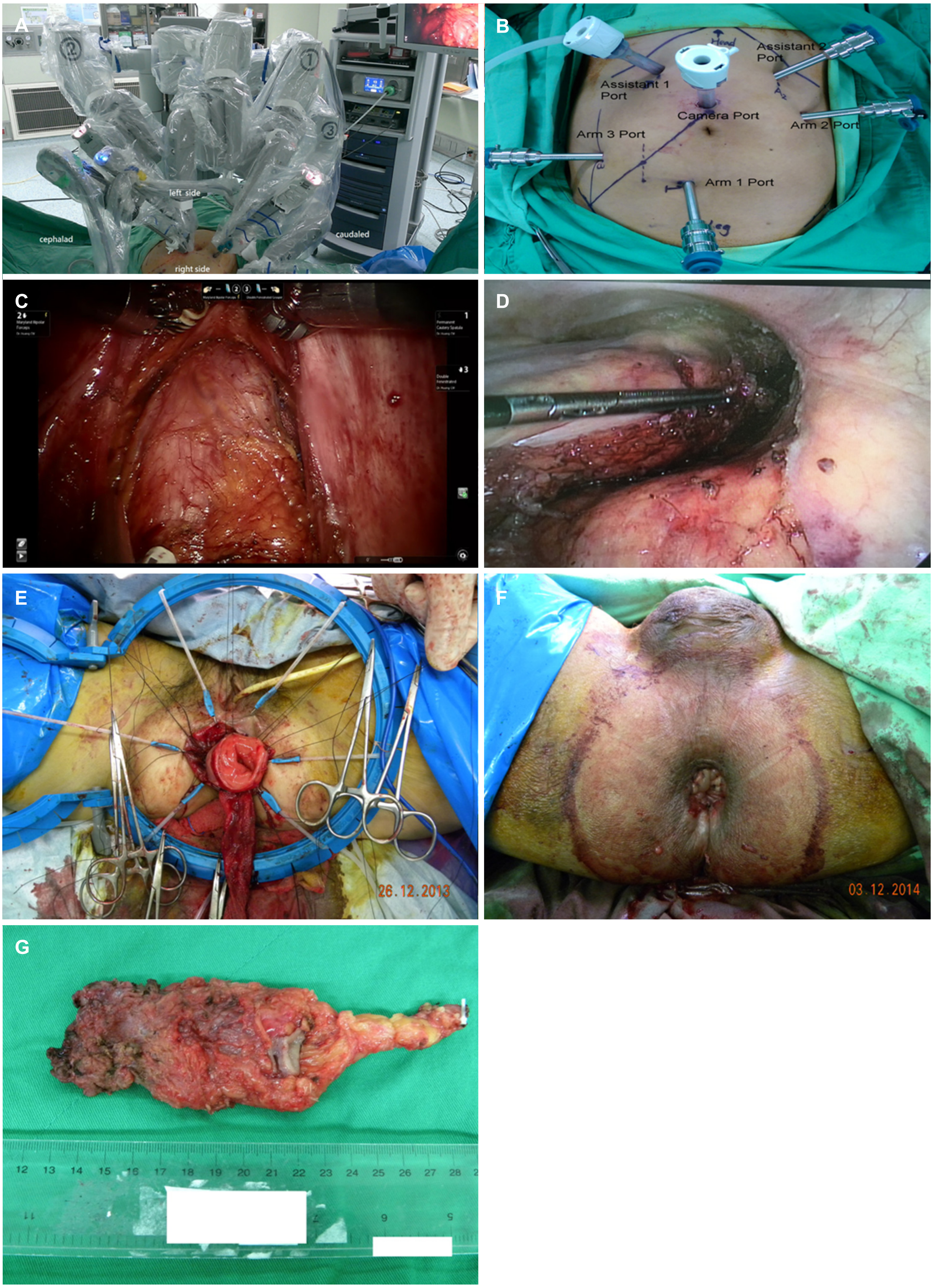

Figure 1. A: Da Vinci docked from patient's left side; B: port positions during single docking; C: intraoperative view of the distal rectum, Da Vinci view; D: intraoperative view of the distal rectum, laparoscopic view; E: intersphincteric resection with long-star retractor; F: coloanal anastomosis done; G: total mesorectal excision specimen

Table 1. Baseline characteristics and perioperative outcomes of 60 patients with low-lying rectal cancer who underwent robotic-assisted total mesorectal excision

Characteristics	Value/number
Age (years, median) (range)	62 (32-87)
Gender	
Female	24 (40%)
Male	36 (60%)
Distance from anal verge (cm, median) (range)	3.5 (1-5)
Pre-operation CCRT	
Yes	49 (81.7%)
No	11 (18.3%)
Pre-operation chemotherapy regimen	49
FOLFOX	36 (73.5%)
Fluoropyrimidine-based	13 (26.5%)
Time interval between radiotherapy completion and robotic surgery (day, median) (range) (49 patients undergoing pre-operation chemotherapy)	91 (47-363)
ASA classification	
II	36 (60%)
III	24 (40%)
BMI kg/m^2 (median) (range)	23.07 (17.50-30.9)
Procedure	
LAR	19 (31.7%)
ISR	37 (61.7%)
APR	4 (6.6%)
Protective diverting colostomy	
Yes	45 (75%)
No	15 (25%)
Docking time (min, median) (range)	5 (3-10)
Console time (min, median) (range)	215 (150-527)
Operation time (min, median) (range)	320 (240-710)
Estimated blood loss (mL, median)	95 (15-450)
Time of first flatus passage (day) (median, range)	2 (1-10)
Time of resuming soft diet (day) (median, range)	4 (2-13)
Postoperative hospital stay (day) (median, range)	6 (5-30)
Postoperative first day VAS pain score (median, range)	3 (1-7)

CCRT: concurrent chemoradiotherapy; ASA: American Society of Anesthesiologists; BMI: body mass index; LAR: low anterior resection; ISR: intersphincteric resection; APR: abdominoperineal resection; VAS: visual analog scale

verting loop transverse colostomy was performed in 45 patients, including 37 patients and 8 patients who underwent ISR and LAR, respectively. The median operating time was 320 min (range, 240-710), with a median blood loss of 95 mL (range, 15-450). Median length of stay was 6 days (range 5-30). No mortality was observed within 30 days following the procedure. Furthermore, no intraoperative complications or conversion to open surgery were noted.

Postoperative complications

Table 2 presents postoperative complications. Three patients required reoperation within 30 days following the procedure, two for anastomotic leak, and one for postoperative bleeding. Transverse loop colostomy was performed for anastomotic leak, and we monitored postoperative bleeding through laparotomy. Other complications included prolonged ileus (n = 3), urethral injury (n = 1), and coloanal anastomosis stenosis (n = 2). We used colonfiberoscope dilation for the two patients with coloanal anastomosis stenosis. The others morbidities recovered uneventfully after conservative treatment.

Pathological and oncological outcomes

The pathological characteristics and oncological outcomes of all 60 patients are listed in Table 3. Preoperative clinical staging demonstrated that the majority of the patients had locally advanced rectal cancer: T3,

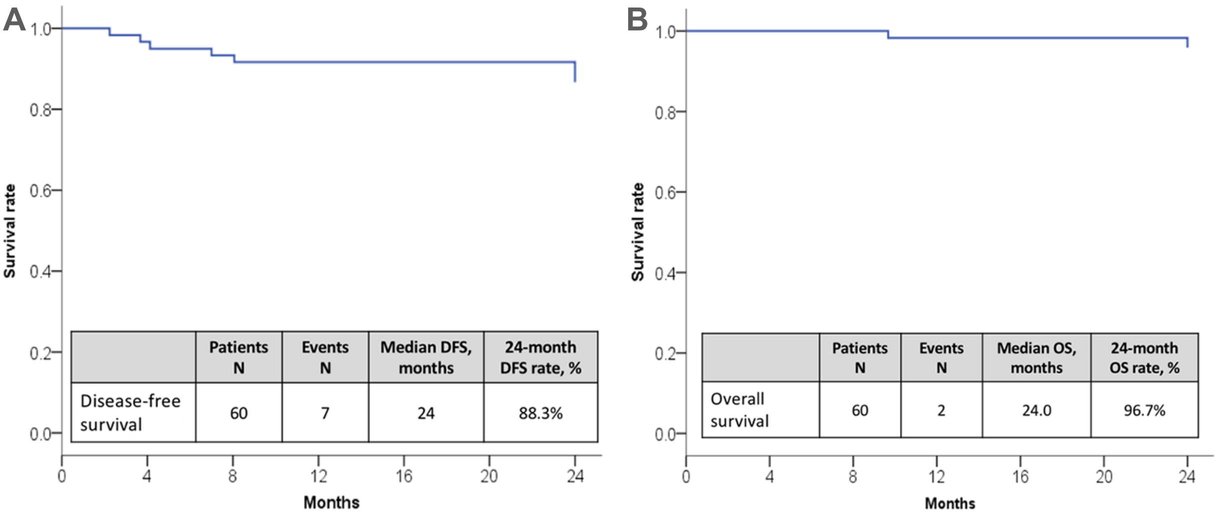

Figure 2. Kaplan-Meier survival curves. A: Disease-free survival; B: overall survival

Table 2. Postoperative complications in 60 patients with low-lying rectal cancer who underwent robotic-assisted total mesorectal excision

Complications	Number (%)	Management
Post-operative bleeding	1 (1.7%)	Laparotomy
Intra-abdominal infection/abscess	2 (3.3%)	1: conservative treatment 1: CT-guided pig-tail drainage
Coloanal anastomosis stenosis	2 (3.3%)	Colonoscopic dilation
Ileus	3 (5%)	Conservative treatment
Anastomosis leakage	2 (3.3%)	Loop transverse colostomy
Urethral injury	1 (1.7%)	Conservative treatment
Pulmonary complication	2 (3.3%)	Conservative treatment
Total	13 (21.7%)	

T4, and N+ in 42 (70%), 8 (13.3%), and 36 (55.8%) patients, respectively. Therefore, preoperative CCRT was performed in 49 patients - the FOLFOX regimen in 36 (73.5%) patients and fluoropyrimidine-based regimen in 13 (26.5%) patients. The median numbers of harvested lymph nodes and apical lymph nodes were 8 (range, 0-36) and 1 (range, 0-6), respectively. However, positive apical lymph node metastasis was observed in only three (5%) patients. The median distances of the DRM and CRM were 1.9 and 1.1 cm, respectively. CRM and DRM were positive in three patients (5%) and one (1.7%) patient, respectively. R0 resection for primary rectal cancer was performed in 57 (95%) patients. Of the 49 patients who received preoperative CCRT, pathologic complete response (pCR) of the primary tumor was observed in 18 patients (18/49 = 36.7%). In total, 19 (38.8%), 17 (34.7%), 10 (20.4%), and 3 (6.1%) patients exhibited complete response [tumor regression grade (TRG) 0], moderate response (TRG 1), minimal response (TRG 2), and poor response (TRG 3), respectively.

During the postoperative follow-up period, 7 patients (11.7%) exhibited cancer recurrence. The median follow-up duration was 28 months (range, 12-53 months). Distant metastasis was observed in 5 patients (1 in the lung, 2 in the liver, 1 in both the lung and liver, and 1 with peritoneal seeding), whereas local recurrence was observed in 2 patients. The overall survival rate at 2 years was 96.7%, whereas the disease-free survival rate at 2 years was 88.3% [Figure 2].

DISCUSSION

Minimal invasive surgery has become the gold standard for colorectal cancer; however, laparoscopy has some limitations. Therefore, a robotic approach to rectal cancer surgery seems appealing. Studies have

Table 3. Clinicopathologic characteristics and oncological outcomes of 60 patients with low-lying rectal cancer who underwent robotic-assisted total mesorectal excision

Preoperative clinical staging	Value/number
Tumor depth	
T1	3 (5%)
T2	7 (11.7%)
T3	42 (70%)
T4	8 (13.3%)
Lymph node metastasis	
N0	24 (40%)
N1	24 (40%)
N2	12 (20%)
AJCC stage (clinical)	
I	7 (11.7%)
II	17 (28.3%)
III	36 (60%)
Postoperative pathological outcomes	
Histology	
Well differentiation	12 (20%)
Moderate differentiation	45 (75%)
Poor differentiation	3 (5%)
Tumor size	
< 5 cm	56 (93.3%)
≥ 5 cm	4 (6.7%)
Tumor size (cm, mean ± SD) (range)	2.11 ± 1.62 (0-8)
Tumor depth	
T0	20 (33.3%)
Tis	1 (1.7%)
T1	9 (15%)
T2	13 (21.7%)
T3	16 (26.7%)
T4	1 (1.7%)
Lymph node metastasis	
N0	46 (76.7%)
N1	12 (20%)
N2	2 (3.3%)
AJCC stage (pathologic)	
0	18 (30%)
I	18 (30%)
II	10 (16.7%)
III	14 (23.3%)
Tumor regression grade (49 patients with preoperative CCRT)	
0	19 (38.8%)
1	17 (34.7%)
2	10 (20.4%)
3	3 (6.1%)
Harvested lymph node (median) (range)	8 (0-36)
Harvested apical node (median) (range)	1 (0-6)
Distance of distal resection margin (cm, median) (range)	1.9 (1.0-4.0)
Distance of circumferential resection margin (cm, median) (range)	1.1 (0.1-3.5)
Distal resection margin	
Free	59 (98.3%)
Positive	1 (1.7%)
Circumferential resection margin	
Free	57 (95%)
Positive	3 (5%)
Resection degree of primary tumor	
R0	57 (95%)
R1	3 (5%)
Oncological outcomes	
Follow-up periods (months, median) (range)	28 (12-53)

R0 resection	57
Locoregional recurrence	2 (3.5%)
Distant metastasis	5 (8.8%)
Lung	1 (1.75%)
Liver	2 (3.5%)
Liver + Lung	1 (1.75%)
Peritoneal carcinomatosis	1 (1.75%)
R1 resection	3
Local recurrence	1 (33.3%)
Lung	1 (33.3%)
Peritoneum	1 (33.3%)

AJCC: American Joint Commission on Cancer; CCRT: concurrent chemoradiotherapy

shown that the robotic approach to colorectal surgery is safe and feasible[16]. Most crucially, favorable short-term clinical and oncological outcomes can be achieved by combining complete robotic-assisted TME with appropriate preoperative CCRT. At least 12 lymph nodes should be examined for each surgical specimen of colorectal cancer, as recommended in the American Joint Commission on Cancer/Union for International Cancer Control guidelines. However, this recommendation was mainly based on studies of colon cancers. Chou *et al.*[17] reported that patients with rectal cancers and older patients who had distally located, early colon cancer were less likely to meet the recommended lymph node yield of 12. Besides, Persiani *et al.*[18] showed that a low lymph node count after neoadjuvant chemoradiotherapy for rectal cancer does not signify inadequate resection or understaging but represents increased sensitivity to the treatment. Additionally, preoperative chemotherapy significantly reduces the number of lymph nodes that can be harvested, with the mean number of detected nodes ranging between 4 and 14 per specimen. In this study, the median number of harvested lymph nodes was 8 (range, 0-36), which is consistent with the literature[18].

The results of this study were consistent with those of a meta-analysis conducted by Scarpinata and Aly[19]. The selection criteria for robotic surgery in this meta-analysis were obesity, male sex, preoperative radiotherapy, and tumors in the lower two-thirds of the rectum. The pCR rate after CCRT observed in our study was 36.7%, which is slightly higher than in previous studies[20,21]. The introduction of oxaliplatin-based chemotherapy and a longer interval may be the major reasons for the higher pCR rate as in our previous study[22]. The sphincter preservation rate achieved in our study was 93.3% (56/60), which is comparable with that reported by Kim *et al.*[23] and Saklani *et al.*[24].

Two pathological assessments appear to be crucial in judging the standard of surgery: CRM involvement and the gross appearance of the surgically resected specimen. Moreover, CRM involvement has been reported as a prognostic factor for local recurrence and survival[25-28]. In this study, the rate of CRM involvement was 5%, with a median distance of 1.1 cm, which is comparable with that reported in other studies (0%-16.1%) [Table 4]. Moreover, the rate of DRM involvement was 1.7%, with a median distance of 1.9 cm, which is also comparable with that reported in previous studies [Table 4]. R0 resection for primary rectal cancer was performed in 57 (95%) patients, 2 of whom developed local recurrence and 5 of whom developed distant metastasis. We attempted to perform R0 resection in all patients, but R1 resection was performed in three patients. One such patient was a 59-year-old woman at clinical stage cT4bN2bM0 with uterus invasion. Neoadjuvant chemotherapy was performed first, followed by robotic ISR 55 days later. The pathology report showed positive CRM, but the DRM was free. During follow up period, she died of intraabdominal infection 2 years and 10 months after operation. The second patient was a 61-year-old man at clinical stage cT4aN2bM0 with visceral peritoneum invasion. Neoadjuvant chemotherapy was performed first, followed by robotic ISR 85 days later. The pathology report showed positive CRM, but DRM was free. During follow up period, he died of pneumonia 9 months after operation. The third patient was a 53-year-old woman at clinical stage cT4bN2bM0 with posterior vaginal wall invasion. Neoadjuvant chemotherapy

Table 4. Comparison of clinical and perioperative outcomes of robotic-assisted total mesorectal excision

Study	Country (year)	Sample size	Lower rectum (%)	Preoperative CCRT (%)	Conversion Rate (%)	Estimated blood loss (mL)	Overall complications (%)	Anastomotic leakage (%)	Rate of sphincter preservation (%)	DRM (cm)	Positive CRM (%)
Present study	Taiwan (2018)	60 (yp Stage 0-III)	100	81.7	0	95	21.7	3.3	93.3	1.9 (1-4)	5
Baek *et al.*[11]	Korea (2011)	41 (yp Stage 0-III)	36.6*	80.5	7.3	200 (20-2000)	22.0	7.3	85.4	3.6 (0.4-10)	2.4
Park *et al.*[12]	Korea (2011)	52 (yp Stage 0-III)	60.4#	23.1	0	NA	19.2	9.6	100	2.8	1.9
Hellan *et al.*[14]	USA (2015)	425 (yp Stage I-IV)	31.3	51.3	5.9	119 ± 164	40.2	8.7	NA	3.0 ± 2.0	0.9
Kim *et al.*[23]	Korea (2016)	33 (yp Stage 0-III)	NA	100	6.1	232.0 ± 180.0	45.6	NA	93.9	2.2 ± 1.5	16.1
Saklani *et al.*[24]	Korea (2013)	74 (yp Stage 0-III)	NA	100	1.4	180 ± 28.1 (0-1100)	16.2	5.4	97.3	1.7 ± 1.4 (0.1-6.0)	4
Pai *et al.*[29]	USA (2015)	101 (yp Stage 0-IV)	28.7	74.3	4	190 ± 128	28.7	6.3	79.2	3.5 ± 2.7 (0.1-16.3)	5
Kim *et al.*[30]	Korea (2016)	60 (yp Stage 0-IV)	56.7*	36.7	0	74.2 ± 50	15	5	93.4	3.1 ± 1.7	11.7
Feroci *et al.*[31]	Italy (2016)	53 (yp Stage (yp 0-III)	NA	49.1	3.8	60.8 (0-400)	26.4	5.7	100	2.5 (0.5-10)	0
Cho *et al.*[32]	Korea (2012)	278 (yp Stage 0-III)	24.8	32.7	0.4	179.0 ± 236.5	25.9	10.4	100	2.0 ± 1.4	5.0
Park *et al.*[33]	Korea (2015)	133 (yp Stage I-III)	24.8	11.3	0	77.6 ± 153.2 (0-700)	19.7	4.5	100	2.75 ± 2.14 (1-14)	6.8
Ghezzi *et al.*[34]	Brazil/Italy (2014)	65 (yp Stage 0-III)	100#	72.3	1.5	0 (0-175)	41.5	7.1	86.2	2.7 (1.6-4.4)	0
Hara *et al.*[35]	Korea (2014)	200 (yp Stage 0-IV)	56.5	27.5	0	190 (0-1500)	38.5	9.5	93.5	1.8 (0-22.0)	1.5
Baik *et al.*[36]	Korea (2013)	370 (yp Stage 0-IV)	26.8	21.1	0.8	245.7 ± 222.1 (10.0-1300.0)	24.6	7.7	99.2	2.6 ± 1.4	6.9
Ahmed *et al.*[37]	UK (2016)	83	NA	21.7	0	10 (0-200)	49	2	88.0	2.7 (0.4-8.0)	3.6
Hellan *et al.*[38]	USA (2007)	39 (yp Stage I-IV)	53.9#	84.6	2.6	200 (25-6000)		12.1	84.6	2.65 (0.4-7.5)	0
Luca *et al.*[39]	Italy (2009)	28 (yp Stage I-IV)	NA	0	0	68 ± 138 (0-600)	NA	NA	75.0	2.5 ± 1.3 (0.6-5.5)	0
Yamaguchi *et al.*[40]	Japan (2016)	203 (yp Stage 0-IV)	60.1#	0.5	0	15.4 ± 26.4	9	1.5	95.1	2.8 ± 1.9	NA
Ramji *et al.*[41]	Canada (2016)	26	NA	58	12	296 ± 155	42	8	85	2.96 ± 2.05	0
Abdel-Gawad *et al.*[42]	Egypt (2014)	55	100	45.4	0	NA	25.5	7.2	100	NA	5.5

*< 7 cm; #extraperitoneal. CCRT: concurrent chemoradiotherapy; CRM: circumferential resection margin; DRM: distal resection margin; NA: not applicable

Table 5. Comparison of short-term oncological outcomes of robotic-assisted total mesorectal excision

Study	Country (year)	Local recurrence (%)	Distant metastasis (%)	Disease-free survival	Overall survival
Present study (low-lying rectum)	Taiwan (2018)	3.5	8.8	88.3% (2-year)	96.7% (2-year)
Pai *et al*.[29] (all rectum)	USA (2015)	4	17	79.2% (3-year)	90.1% (3-year)
Kim *et al*.[30] (all rectum)	Korea (2016)	1.9	26.4	72.8% (4-year)	87.7% (4-year)
Feroci *et al*.[31] (mid and low-lying rectum)	Italy (2016)	1.9	17	79.2% (3-year)	90.2% (3-year)
Cho *et al*.[32] (all rectum)	Korea (2012)	1.8	12.2	81.8% (5-year)	92.2% (5-year)
Park *et al*.[33] (all rectum)	Korea (2015)	2.3	12.0	81.9% (5-year)	92.8% (5-year)
Ghezzi *et al*.[34] (low-lying rectum)	Brazil/Italy (2014)	3.2	18.5	73.2% (5-year)	85.2% (5-year)
Hara *et al*.[35] (all rectum)	Korea (2014)	4.5	10	81.7% (5-year)	92.0% (5-year)
Baik *et al*.[36] (all rectum)	Korea (2013)	3.6	17.6	79.2% (3-year)	93.1% (3-year)
Abdel-Gawad *et al*.[42] (low-lying rectum)	Egypt (2014)	14.8	14.4	82.6% (3-year)	88.7% (3-year)

Table 6. Comparison of short-term oncological outcomes of low-lying rectal cancer

Study	Country (year)	Local recurrence (%)	Distant metastasis (%)	Disease-free survival	Overall survival	Surgery method: open (%)	Surgery method: laparoscopic (%)	Surgery method: robotic (%)
Present study	Taiwan (2018)	3.5	8.8	88.3% (2-year)	96.7% (2-year)	0%	0%	100%
Ghezzi *et al*.[34]	Brazil/Italy (2014)	3.2	18.5	73.2% (5-year)	85.2% (5-year)	37.3%	0%	62.7%
Abdel-Gawad *et al*.[42]	Egypt (2014)	14.8	14.4	82.6% (3-year)	88.7% (3-year)	NA	NA	0%

NA: not applicable

was performed first, followed by robotic ISR 203 days later. Pathology reports showed that both CRM and DRM were positive. During follow up period, she was still alive 2 years after operation.

In our study, none of the surgical procedures were converted to open or laparoscopic surgery. Studies have shown that advanced local cancer stage, bulky tumors, and high body mass index may be responsible for conversions[14,23,31,38]. Although our study consisted of some difficult cases, including large tumors (4 patients with a tumor size > 5 cm), low-lying rectal cancer (distance of 3.5 cm from the anal verge), a greater proportion of men (36 patients), and more challenging operation requirements (37 patients with intersphincteric dissection), our morbidity results appeared promising. The anastomosis leakage rate in our study is 3.3%, which is slightly lower than that in other studies [Table 4].

This study had some limitations. First, this was a single-institution retrospective study consisting of only 60 patients. Second, the follow-up interval was short, with a median follow-up duration of 28 months; thus, only short-term (2-year) survival and oncological outcomes are reported. Nevertheless, the 2-year overall survival (96.7%) and disease-free survival (88.3%) in our study were consistent with those reported in previous studies [Table 5]. We also compared the short-term ontological outcomes of low-lying rectal cancer [Table 6]. Third, we did not evaluate the postoperative outcomes with regard to urinary and sexual functions.

In conclusion, through comparison of short-term clinical outcomes, we have demonstrated that the robotic TME technique is safe and feasible for patients with low-lying rectal cancer. Moreover, combining this approach with appropriate preoperative CCRT can deliver favorable short-term oncological outcomes. However, further investigation of long-term oncological outcomes is required using studies with longer follow-up durations.

DECLARATIONS

Authors' contributions

Conception and design of the study, Data analysis and interpretation: Chen PJ, Huang CW, Tsai HL, Yeh YS, Wang JY

Data acquisition, provided administrative, technical, and material support: Su WC, Chang TK, Huang MY, Huang CM, Wang JY

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
This study was approved by hospital ethics committee of Kaohsiung Medical University Hospital. Consent to participate was obtained.

Consent for publication
Not applicable.

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Mini-invasive Surgery

Review

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Theranostic nanoplatforms for treatment and diagnosis of rectal and colon cancer: a brief review

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Abstract
Colorectal cancer (CRC) is a common health problem due to its high prevalence and high mortality rate. Adjuvant and neo-adjuvant strategies, chemotherapy and radiotherapy alone or in combination, have substantially improved survival and local recurrence rates. Their effectiveness remains limited due to the intrinsic build-up of resistance of cancer cells to chemotherapy drugs, dose-limiting toxicities and other major side effects. New strategies to overcome these issues are being developed, one of which is cancer nanomedicine, a rapidly developing interdisciplinary research field. The last few decades have seen a rapid growth of interest in utilising nanoparticles and nanotechnology in cancer medicine. This is mainly due to the suitable physical and chemical properties of nanoparticles for in vivo applications. Cancer nanomedicine for targeted drug delivery and imaging has been widely investigated preclinically and clinically. Nanomedicine has been considered as a novel solution to enhance CRC diagnosis and treatment, both separately and in combination using theranostic techniques. This review highlights the research, opportunities, and challenges for the development of nanoplatforms for diagnosing and treating CRC.

Keywords: Nanomedicine, colorectal cancer, nanoparticles

INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer in the world[1-3]. In stage III rectal cancer surgical resection followed by adjuvant chemotherapy, and of late neo-adjuvant chemo-radiotherapy in locally advanced disease, survival rates up to 58% at 5 years[3-6] have been reported. Recurrence, local and/or distant, may occur in up to approximately 50% of patients, but 5-year survival if curative re-resection or R0 metastasectomy is achieved, may still be from 22%-49%[7,8]. In primary CRC survival is very much stage dependent and varies from 90% 5-year survival rate in stage I rectal cancer to less than 10% of people diagnosed with distant metastatic cancer[6,9]. Lymph-node (LN) metastases are the most powerful predictor of survival and need for adjuvant treatment in all solid cancer and almost always follow a well-defined tumour-draining lymph node basin[10]. Due to their small size and poor vascularisation, LN metastases are difficult to detect with certainty using conventional imaging modalities. Given that chemotherapy and radiation in the (neo-) adjuvant setting have their specific adverse effects and limited efficacy profile, it is imperative to increase the diagnostic accuracy of LN metastases in the pre-operative setting[11]. Nanomedicine may offer an alternative and potentially may be more effective in diagnostics. In combination with therapeutics, it may offer a less toxic theranostic pathway[12-20]. The present paper highlights the current understanding of nanomedicine and its role in the management of CRC, and rectal cancer in particular. Nanomedicine is in its adolescence and is slowly transitioning from cell and animal studies towards human trials. To develop appropriate first-in-human trials it is important for clinicians to understand the variety of nano-platforms and particles currently available along with their specific features.

NANOMEDICINE

The ability to explore the structure and characteristics of materials at the nanoscale has made a great change in many fields of science such as medicine. In the comparison of nanoparticles to their bulk systems, the main properties of nanoparticles that make them fundamentally different in their behaviour are surface-related characteristics and quantum characteristics[21-25]. Efficient drug and medical radioisotopes loading (due to the highly reactive surfaces of nanoparticles) in combination with unique physical (e.g., magnetic) properties of nanoparticles have led to rapidly growing interest in nanoparticles for medical applications such as drug delivery and imaging[26-33]. Particles or molecules with 10-100 atoms (at least in one dimension) are normally regarded as nanoparticles[34-37] [Figure 1]. Generally, nanoparticles are sized between 1-100 nanometers. Nanoparticles compared to their bulk system (e.g., microparticles) have high surface area-to-volume ratio. Therefore in a nanoparticle, the number of atoms at the surface is greater than those within their internal core and consequently they have a high number of interaction sites available at the surface which makes them chemically more reactive[38]. Moreover, at nano-scale where the size of particles (e.g., nanocrystal) is comparable to the de Broglie wavelength of an electron, the change in electronic energy levels become discretely discrete, a condition known as the quantum confinement of the electron wave function[39]. This effect is responsible for some of the unique behaviour (e.g., optical) of nanoparticles such as quantum dots. These unique properties (e.g., optical, magnetic, active surface) give nanoparticles the potential to be used as a diagnostic agent or carrier for delivering therapy and thus to be an ideal platform for developing theranostic nano-agents in medicine.

NANO-PLATFORMS FOR DRUG DELIVERY

Tumour tissues of different cancer types such as colon, breast, prostate and lung cancer are permeable to nano-molecules and nanoparticles[40-42]. This is due to their distinctive structural characteristics such as the hyper-permeable vasculature and impaired lymphatic drainage[40,43,44]. Nanoparticle and nano-molecule drug delivery mechanisms can be classified into active and passive targeting. Active targeting highly depends on the interaction between the target cell receptors and nanoparticles whereas passive targeting relies on a number of factors such as longer biological half-life, long-circulating time at tumour locations and the flow rate of nanoparticles to the impaired lymphatic system[45-49]. Moreover, the enhanced permeability and retention effects and nanoparticle clearance by the mononuclear phagocyte system play an important role in determining the effectiveness of the nano-platform drug delivery system[44,50]. The reticuloendothelial system (RES) effect is one of the most common problems among all different

Table 1. Current nanoplatforms under preclinical development for colorectal cancer[58-62]

Formulation	Ligand	Target
Nanosized particle	Antibody	Carcinoembryonic antigen (CEA)
Dextran and PEG-coated superparamagnetic iron oxide nanoparticles	Single-chain Fv antibody fragment (scFv)	CEA
Gold and iron oxide hybrid nanoparticle	scFv	A33 antigen
Polymer capsules	Humanized A33 monoclonal	Fas receptor
Chitosan nanoparticles loaded with 5-aminolaevulinic acid	Folic acid	HT29 colorectal cancer cell lines overexpressing folate
HPMA-copolymer-doxorubicin conjugates	Peptide GE11	A431, HT29 and SW480 cell lines
Mesoporous silica nanoparticle	Coated with poly-(L-lysine) and hyaluronic	HCT-116 cancer cells

PEG: polyethylene glycol; HPMA: hydroxypropyl methacrylate

types of nanoparticles. RES effect refers to the quick absorption of nanoparticles by macrophages which usually results in clearing nanoparticles from the circulation *in vivo*[51-53]. Specific types of nanoparticle coating may prevent and minimise the RES effect. Nanoparticles with surfactants or covalent linkage of polyoxyethylene have shown to effectively minimise the RES effect[54]. The size and shape of nanoparticles are the other two main factors that affect the delivery of conventional therapeutics to solid tumours. Nanoparticles larger than 500 nm are shown to be rapidly removed from the circulation *in vivo*[44,55]. In addition, targeted nanoparticles as a drug delivery system based on monoclonal antibodies are currently one of the main approaches for CRC therapy under preclinical development[56,57]. A list of these nanoplatforms is presented in Table 1.

LIPOSOMES-BASED NANOPARTICLES

The first therapeutic nano-platform applied in medicine was introduced by Bangham *et al.*[63] in 1961. This nano-platform was based on liposomes which were the first drug-delivery system approved by FDA for clinical practice. Liposome-based nanoparticles are one of the commonly used nanoparticles for delivering small peptides, nucleic acids, and proteins in nano-platform drug delivery[64-66]. Nanoliposomes are non-toxic, spherical nano-carriers containing an aqueous core with phospholipid bilayer[67,68]. Nanoliposomes are considered as one of the most effective drug delivery systems at a cellular level. This is mainly due to their size, ability to incorporate various substances and slow-releasing and targeting characteristics which also results in decreasing side effects[69,70]. There are three main types of nanoliposomes: (1) stealth liposomes or long-circulating liposomes, which have a modified phospholipid bilayer structure and added gangliosides or a polyethylene glycol (PEG) to assist avoiding blood plasma opsonins proteins binding to the liposome surface and minimise the RES effect; (2) active nanoliposomes: this type of nanoparticle targets receptors, hormones, peptides and antibodies; and (3) sensitive nanoliposomes: they are special active nanoliposomes with unique properties such as pH-sensitive, thermo-sensitive and magnetic[21,70,71]. Doxorubicin (Doxil®)-liposome is an example of FDA approved nanoliposome for chemotherapy for CRC[72]. Doxil is approximately 100 nm and although it has much less gastrointestinal and cardiac toxicity, it causes other side effects such as redness and peeling of the skin[73]. Marqibo® is another recent nanoliposomal drug approved by FDA[74-76]. Marqibo is approximately 100 nm and it is a cell cycle-dependent anticancer drug. Thermo-sensitive liposome doxorubicin (Thermodox®) is another promising nanoliposomal drug for colorectal liver metastases in combination with radiofrequency ablation[77]. Thermodox® is a nanoliposomal with doxorubicin formulation which releases the drug upon a mild hyperthermic trigger[77]. Thermodox can deliver 25 fold more doxorubicin into tumours than IV doxorubicin does[77].

CORE-SHELL NANOPARTICLES

There has been an increasing interest in developing and synthesizing core-shell nanoparticles[78,79]. The core-shell nanoparticles are composed of two or more materials which can be synthesised with different

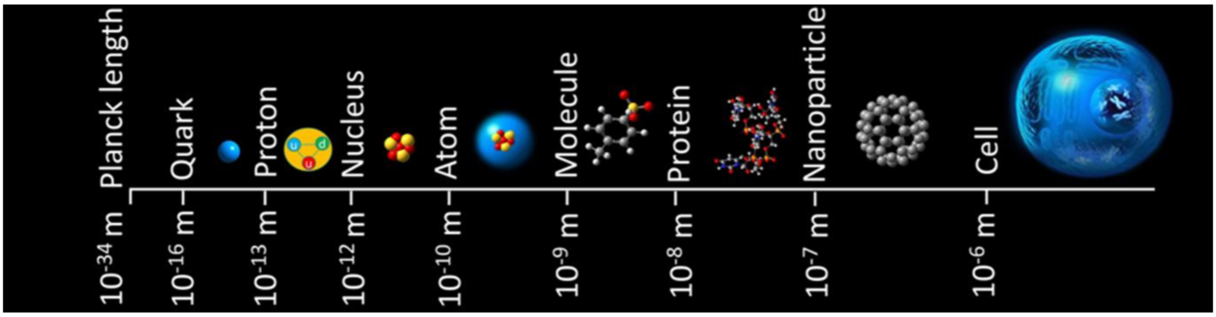

Figure 1. Illustration of relative sizes of objects

combinations of inorganic and organic materials[80]. To enable efficient surface modification, increasing the functionality and stability, the core nanoparticles is coated. The core-shell has different applications in the medical field such as controlled drug delivery, multimodal-imaging, cell labelling and nuclear medicine therapy[81,82]. Superparamagnetic iron oxide nanoparticles (SPIONs) are one of the most common core-shell nanoparticles that are used in medical imaging and therapy[83-93].

SPIONS

SPIONs are nanoparticles that have become the focus of nanomedicine research since 1980[94], and have evolved to include SPIONs with a biocompatible polymer coating and core surface modification specifically for nanomedicine and nuclear medicine applications. The key features of SPIONs include exhibiting magnetisation only in an applied magnetic field and the ability to load drugs and medical radioisotopes (due to their highly active surface). Over the past few decades, further developments in radiochemistry and radiation sciences have led to applying the field of nanomedicine to nuclear medicine for enabling multimodal medical imaging (radiolabelled nanoparticles with imaging isotopes) and radionuclide therapy (radiolabelled nanoparticles with therapeutic isotopes) of different types of cancer. This has significantly improved cancer diagnosis and therapy[95]. Currently nanoparticle-based magnetic resonance imaging (MRI) is utilised in cancer medicine for enhancing the MR image contrast. There are key advantages of SPION drug delivery including longer circulation half-lives, improved pharmacokinetics, capability to carrying a large amount of drugs, reduction in side effects and targeting the drug to a specific location in the body[26,38].

Additionally, the doped gold-SPIONs have been developed for targeted photothermal therapy for destruction of CRC[96]. The developed gold-SPIONs were also functionalised with a single chain antibody to enable active targeting of the A33 antigen, which is overexpressed in CRC cells. Results demonstrated that the internalisation of gold-SPIONs was five times faster for cells expressing the A33 antigen than cells not expressing the antigen. Furthermore, this study has shown that upon 6 min of laser radiation exposure (with an 800 nm laser at 5.1 W·cm^{-2}), 53% A33-expressing cells died whereas only 5% of A33 non-expressing cells died. These results demonstrated an excellent selectivity for targeting and killing CRC.

Moreover, SPION-based MRI has emerged as a common approach in medical imaging specifically of lymph nodes in solid cancers, including CRC[97]. This caused by a preferential uptake of SPIONs in lymph node as well as the ability of SPIONs to produce high contrast between cancerous and healthy tissues[96]. Due to the physical and chemical properties (e.g., highly reactive surface and magnetisation) of SPIONs, they have attracted enormous attention in cancer diagnosis and therapy[83-93]. SPIONs *in vivo* can perform actively (targeting a tissue or an organ) or passively. Peptide or antibody labelled SPIONs act as an active carrier for targeting the organ or tissue of interest. However, passive SPIONs mainly rely on the polymer type and particle size to achieve accumulation at the target site. Hydrophilic SPIONs with dextran and

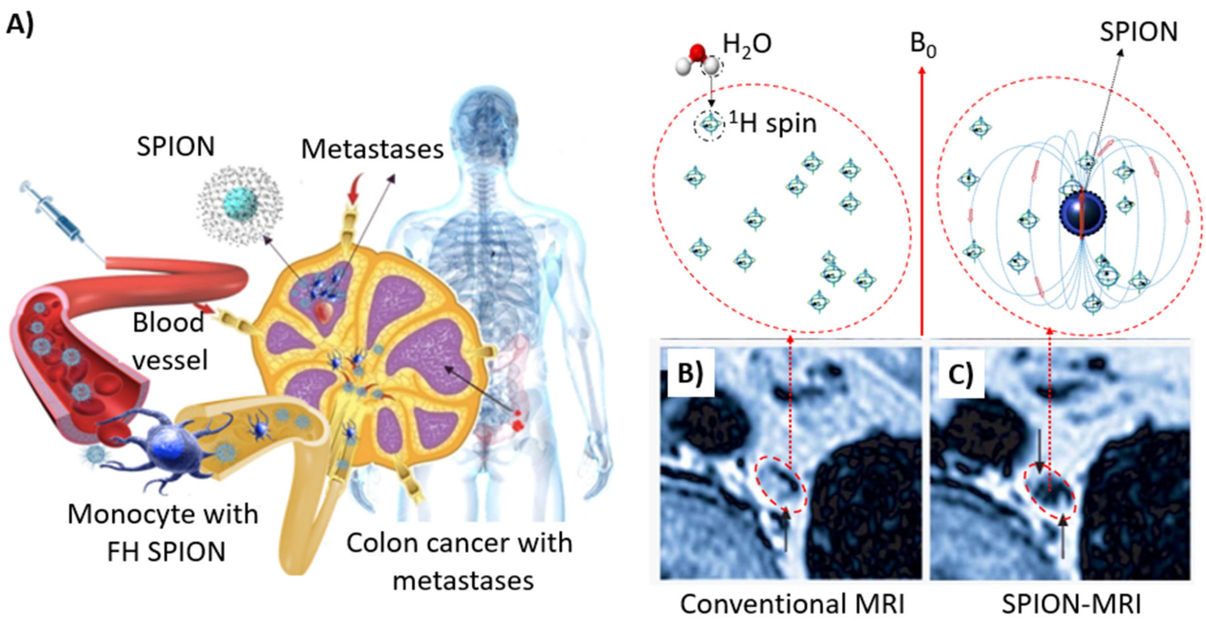

Figure 2. A: Following intravenous injection, SPIONs slowly extravasate from vascular space to interstitial space, from where they can be taken up by immune cells (monocytes/macrophages) and delivered via lymphatic vessels to lymph nodes. The SPIONs remain in normal nodal tissue and reduce MRI signal intensity, thereby enhancing contrast against any metastatic lesions in the node; B and C: demonstrating the mechanism of negative contrast agent, SPIONs in lymph node imaging; B: a conventional T2-weighted MR image of the lymph node showing the whole lymph node is associated with cancer metastases; C: the T2-weighted MR image of the lymph node with enhanced contrast produced by SPIONs showing only two small metastatic regions (e.g., hyper intense foci). The MR images in B and C were reproduced[96]. SPION: superparamagnetic iron oxide nanoparticle; MRI: magnetic resonance imaging

PEG surfaces are able to evade the RES as well as resisting the opsonisation (destruction by an immune cell) which leads to the increase of their biological half-life (circulation time) and the probability of targeting a specific cell[98-100]. Moreover, SPIONs with a size of less than 30 nm can also slowly extravasate from vascular space to interstitial space, from where they can be taken up by immune cells (monocytes/macrophages) and delivered via lymphatic vessels to lymph nodes. These passive SPIONs can remain in normal nodal tissue and reduce MRI signal intensity, thereby enhancing contrast against any metastatic lesions in the node [Figure 2].

CONCLUSION AND FUTURE DEVELOPMENT

Nanoplatforms constitute valuable drug delivery systems that have been shown to serve the dual purpose of improving diagnostic accuracy and therapeutic effectiveness for CRCs. Cancer nanomedicine is a rapidly developing interdisciplinary research field that may have a transforming effect on diagnostic accuracy, toxicity and drug delivery specifically in rectal cancer. Finally, cancer nanomedicine for targeted drug delivery and enhanced imaging holds great promise and is moving from basic cell line research and subsequent animal studies work into the next stage of the translational pipeline: first-in-human trials.

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Authors' contributions

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Mini-invasive Surgery

Review

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Complications of laparoscopic rectal cancer surgery

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Abstract

Laparoscopic rectal cancer surgery has widely been adopted over the past decade. With technical advances, data have shown equivalent outcomes with open surgery. In this paper, we discuss the potential complications of laparoscopic anterior resection, the need for early recognition and prompt management.

Keywords: Rectal cancer, postoperative complications, laparoscopic anterior resection

INTRODUCTION

Laparoscopic anterior resection (LAR) is currently a routine practice in specialized high-volume centres, with equivalent oncological outcomes in historical, open surgery[1-3]. Appropriate pelvic dissection can be measured by the adequacy of circumferential margin (CRM) and distal margin, both are risk factors of local recurrence. No difference in CRM positivity has been shown in patients undergoing open and LAR in the large, multicentre randomised controlled trials, such as the CLASSIC trial[1] (14% *vs.* 16%, respectively). LAR remains a technically challenging technique, particularly in the male pelvis, because of limited space in the pelvic cavity. It is estimated that a learning curve of 60-80 resections are required to obtain proficiency[4]. Data suggest that the learning curve is an important risk factor for postoperative complications[5].

Similarly, many data exist to suggest that postoperative complications may promote tumour recurrence and decrease long-term survival[6,7], although there is no general consensus among patients undergoing low anterior resection for rectal cancer[8]. Post-operative complications can be classified according to time-line related to surgery[1,8], although most authors use well-known classification systems such as Clavien-Dindo[9] [Table 1].

Table 1. Classification of post-operative complications according to Clavien-Dindo

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
IV	Life-threatening complication, requiring IC/ICU management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of patient

IC: intermediate care; ICU: intensive care unit

EARLY POSTOPERATIVE COMPLICATIONS

Morbidity rates occurred within 30 days of the LAR ranged from 25%-32%[1,8] while mortality during the same period reaches 6% to 8%[5,8].

Surgical site infection

Surgical site infection (SSI) includes incisional or wound infection and organ space infection occurring within 30 days after surgery.

Incisional SSI

Incisional SSI is further divided by the Centres for Disease Control and Prevention[10] into superficial incisional SSI, involving only the skin and subcutaneous tissue, and those involving deeper soft tissues, known as deep incisional SSI. Wound infection is defined by the presence of purulent drainage from the superficial incision with organisms isolated on its culture and signs or symptoms suggestive of infection, such as erythema, induration and pain. Superficial SSI is one of the most common complications after anterior resection, being described in 6%-10% of cases[1,2]. A multivariate analysis showed that wound infection was related to tumour stage, a converted laparoscopic procedure and open surgery[11]. The use of 2% chlorhexidine gluconate in 70% isopropyl alcohol skin preparation before surgery may reduce the rate of SSI in clean-contaminated surgery compared to povidone-iodine, supported data from two systematic reviews and meta-analysis, albeit with limitations in data interpretation due to heterogeneity[12,13].

Organ space SSI

Organ space SSI includes anastomotic leakage (AL) and any intra-abdominal or pelvic abscess diagnosed with radiological examination or reoperation, with the presence of purulent discharge from a drain, confirmed by laboratory culture. This broad definition makes its interpretation and comparison between series of patients difficult, with the uncertainty of whether a pelvic abscess occurs in the presence of, or absence of, anastomotic insufficiency[11].

The rate of intra-abdominal or pelvic sepsis after rectal cancer resection varies between series, but is generally accepted to occur in between 12%-17% of patients[14,15]. In the presence of a localized abscess, a percutaneous computed tomography (CT)-guided drain placed in interventional radiology combined with intravenous antibiotics is the cornerstone of management. Transrectal or transperineal ultrasound-guided drainage may also be utilized for pelvic sepsis in the presence of a low anastomotic leak[16]. Where an abscess is not suitable for percutaneous drainage or there is an absence of radiological expertise, surgical lavage should be considered, which can be facilitated laparoscopically with good control of sepsis[8].

Anastomotic leak

The most common postoperative complication after LAR is AL, with an incidence of 5.5%-8% with significant impact on morbidity and mortality[1,3]. There is a wide variability in the terminology used in

Table 2. Risk factors associated with anastomotic leakage

Modifiable risk factors	Non-modifiable risk factors
Smoking or previous smoking	Male gender
Obesity	Age > 60 years
Alcohol (> 21 units per week)	Previous radiotherapy
Neoadjuvant radiotherapy	ASA grade score > II
Immunosuppressant treatment	Comorbidities
Malnutrition	Diabetes mellitus
Preoperative weight loss > 10%	Renal disease
Hypoalbuminemia	COPD
	Vascular disease
	Emergency surgery
	Distal anastomosis
	Advanced neoplasia
	Intraoperative blood loss > 100 mL
	Blood transfusion

ASA: American Society of Anaesthesiologists; COPD: chronic obstructive pulmonary disease

the literature, which makes comparison difficult, but it is widely agreed that an AL is a breach in a surgical anastomosis between two hollow viscera, with or without luminal content extravasation[17]. Male gender and low anastomosis are risk factors of AL after an anterior resection; probably because of narrower pelvis in the male, and suboptimal blood supply for distal anastomoses[17-19]. In a multivariate analysis performed with data from the Swedish rectal cancer registry, level of anastomosis ≤ 6 cm, American Society of Anaesthesiologists grade > 2, and severe bleeding were identified as risk factors of AL[19]. Other risk factors associated with AL are immunosuppression, obesity, current or previous heavy smoking and malnutrition[17,18] [Table 2]. Preoperative radiotherapy was previously postulated as being etiologic[18], but larger randomised controlled trials, such as The Medical Research Council CR07 and National Cancer Institute of Canada Clinical Trials Group C016 showed no difference of AL between patients undergoing anterior resection with or without neoadjuvant radiotherapy with patients who had postoperative chemoradiotherapy[20].

The use of preoperative mechanical bowel preparation, remains controversial, and a recent review of 1,369 patients who underwent elective rectal cancer resection demonstrated a significantly lower rate of clinical anastomotic leak in the group who had surgery without mechanical bowel preparation[21]. The value of a defunctioning stoma is still not clear. Some studies defend that a diverting stoma does not prevent AL, rather it facilitates management of the consequences of a leak; therefore, the use of a diverting stoma is a safe option in high-risk patients[19]. However, two meta-analyses[22,23] reported a significant benefit of defunctioning stoma reducing the rate of AL and reoperations related to leakage, although the number of randomized control trials included in both studies was small. It has been suggested that the use of pelvic drainage after anterior resection may detect early AL, reducing the incidence of pelvic sepsis and decreasing the need of reoperation. However, some studies have reported potential risks related to the use of pelvic drains such as bowel perforation, vessel injury, infection around the site of its entrance, and pain[15]. Recently, a prospective randomized trial showed no benefit in reduction of pelvic sepsis or in the time to diagnosis the AL among patients with suction pelvic drain after rectal excision for cancer[24]. Some groups support the use of laser fluorescence angiography intraoperatively in order to evaluate perfusion of the proximal colon prior to creation of the anastomosis[25], but level 1 evidence is required before this becomes universally accepted as a standard practice. There is consensus that a surgical anastomosis should be tension-free with good blood supply, often necessitating splenic flexure mobilisation and inferior mesenteric vein ligation under the inferior border of the pancreas[18].

Early diagnosis of AL is critical to managing the ensuing pelvic sepsis and treating high-risk patients[17]. Classically, an anastomotic leak is diagnosed between postoperative day 6 to 9, although the range is wide[26]. An abnormal abdominal examination, in addition to increased systemic inflammatory response

Figure 1. Anterior defect on end-to-end stapled anastomosis with a faecal collection

syndrome after an anterior resection should prompt a high index of suspicion of an AL, but some leaks can present with a more insidious course and become evident later, presenting as a pelvic abscess or with the presence of faeces in the pelvis[16] [Figure 1]. In order to detect AL promptly, some earlier indicators are used. A systematic review and meta-analysis performed with 2483 patients following colorectal surgery showed that serum C-reactive protein concentration measured on day 3-5 after resection is a useful negative predictive test but not a good positive predictor of AL, although included studies did not distinguish between colonic and rectal resection[26]. In patients who are not systemically unwell or unstable, a CT with water-soluble contrast enema may confirm the clinical suspicion of AL, with a sensitivity of 0.91, but the appearance of an intact staple line does not rule out an AL, with high false-negative rates reported in the literature[27]. This may be related to the fact that post-operative CT may be performed before there is radiological evidence of AL[17].

A disrupted colorectal anastomosis can be salvaged in the majority of cases often utilising minimally invasive techniques; however, in a haemodynamically unstable patient an emergent laparotomy is mandatory[8]. Laparoscopy enables the surgeon to assess the peritoneal cavity and the status of the anastomosis[16,28] with faster recovery in selected patients[29]. However, there is no clear evidence of superiority to open surgery[30]. Among the methods used to manage AL, diverting stoma with peritoneal lavage with or without intra-abdominal drain placement was the most common method of managing AL[30]. Small leaks (< 30% of the circumference) could be treated with primary repair of the anastomosis with a defunctioning stoma, while in case of severe peritoneal contamination with large AL or colonic ischaemia, a Hartmann's procedure is recommended[8]. A transanal approach with anoscopy is an option in order to perform a primary repair on a low anastomosis (< 5 cm from the anal verge) while a transanal endoscopic approach is recommended for higher anastomosis (anastomosis ≥ 5 cm from anal verge)[28]. The transrectal ultrasound-guided drainage performed by interventional radiologists has good results, as mentioned in "Organ space SSI"[16] and in case of sinus persistence, the use of an endo-sponge is a good alternative, avoiding protecting stoma in some scenarios. This device is inserted transanally, after washing the cavity, and attached to a low vacuum wound drainage system enhancing granulating tissue and cavity closure[31].

Haemorrhage

Intraoperative bleeding is the most common intraoperative complication[1], and may be difficult to manage with fatality imminent if not rapidly controlled. Pelvic haemorrhage can occur with injury of the presacral venous plexus (PSVP) and the sacral basivertebral veins if dissection is posterior to the mesorectal plane, behind the pre-sacral fascia, occurring in 4.6% to 9.4% of cases[32]. PSVP is formed by the two lateral sacral veins and the middle sacral vein, anastomosing with the internal vertebral system through the basivertebral vessels emerging from the sacral foramina. It is localised underneath the presacral fascia, being easily lacerated, with high propensity to bleed[33]. Managing bleeding from the pre-sacral veins is challenging; conventional methods such as direct sutures often fail and may exacerbate bleeding. It is often necessary to pack the pelvis with large swabs, the direct pressure arresting haemorrhage. A "second-look laparotomy" is required in 24-48 h to remove the packs, as leaving a large volume of foreign body *in situ* can increase the risk of pelvic sepsis[34]. Sterile thumbtacks could be used as an alternative, but they are ineffective in case of diffuse haemorrhage, and some authors report chronic pain and anastomotic fistulas related to their placement in the presacral space[33]. Other techniques have been suggested such as topical haemostatic agents[32], direct or indirect coagulation with spray electrocautery, argon or bipolar coagulation. Suture ligation of the presacral veins in circles with 4-0 silk suture thread is an alternative with good control of bleeding if other techniques fail[34].

Iatrogenic splenic injury is described in 2% of left-sided colonic resections, caused by inadvertent traction or capsular tear due to adhesions during splenic flexure mobilization[35]. Splenectomy is typically a last resort, with spleen conserving manoeuvres such as splenorrhapy or application of topical haemostatic agents preferable, as splenectomy has life-long implications for patients such as overwhelming post-splenectomy infection (OPSI). In order to prevent OPSI, the polyvalent pneumococcal vaccine, *Haemophilus influenzae* type b conjugate vaccine and the meningococcal polysaccharide vaccine are administered within 2 weeks of splenectomy. The use of antibiotics might reduce but not abolish OPSI, although it's use is based on limited evidence[36].

Limited haematochezia with the first bowel movement is not unusual after surgery, described in 6.5% of cases[37], but severe bleeding can be quite challenging because of the risk of compromising a healing anastomosis. Treatment should initially involve prompt resuscitation, including blood transfusion depending on patient's clinical status, age and comorbidities. If bleeding per rectum does not stop spontaneously, endoscopic assessment of anastomosis is undertaken, with copious lavage reported as being successful in securing haemostasis, reserving surgical intervention when there is failure to arrest bleeding or haemodynamic instability[37,38]. When dealing with low anastomoses, an examination under anaesthesia with transanal suture placement or rectal packing is effective. If these measures fail, one is committed to taking down the anastomosis.

Urinary injury

Urinary injury, namely to the bladder or ureter, occurs in 2%-2.8% of LAR[1,39]. Ureteric injury may occur during the mobilisation of sigmoid colon, when elevating the mesocolon off the retroperitoneum or along the lateral pelvic sidewall, on entry into the pelvis[39]. Ureteral injury may be diagnosed intraoperatively, but unfortunately, 50%-70%[40] of cases the diagnosis is made post-operatively with a high volume of serous fluid in the pelvic drain with low urinary output or localised peritonitis. To confirm ureter disruption, a cystoscopy and a retrograde pyelogram can be performed, ideally following a CT-Urogram[40].

If diagnosed intra-operatively, the ureter may be repaired primarily with an end-to-end anastomosis over a JJ-ureteral stent with absorbable sutures; some authors reporting this successful approach laparoscopically[8]. When a long defect is discovered, or the ureter has been transected using an energy device, management is dictated by the location of the defect, techniques such as the ureteroneocystostomy with or without vesico-psoas hitch or a Boari tubularized flap may be required[40].

Bladder injury is commonly associated with electrocoagulation tears during the dissection of the rectum anterior wall. Intermittent suturing with absorbable sutures and leaving of urethral catheter *in situ* for 7-10 days is necessary[40]. A post-operative cystogram is mandatory prior to removing the urinary catheter. Where there is suspicion of urinary tract injury administration of intravenous indigo-carmine or methylene blue, which are excreted in the urine, may be beneficial in identifying a defect[41].

Postoperative ileus. Intestinal obstruction

Postoperative ileus (POI) is defined as a transient cessation of coordinated bowel motility after surgical intervention, which prevents the effective transit of intestinal contents or tolerance of oral intake[42]. POI can be secondary of an intra-abdominal complications such as an abscess or AL, but may occur ab-initio, in the context of surgical stress response, which stimulates inhibitory reflexes and releases inflammatory mediators resulting in impaired bowel motility[43].

Some authors have suggested that laparoscopic surgery is associated with less frequent POI compared to open surgery due to the minimal intestinal manipulation leading to decreased local inflammatory response[3,5]. However, there is a dearth of evidence and no accepted consensus that laparoscopic surgery in major colorectal surgery is protective against POI[1]. To date, no good pharmacological treatment is available to diminish POI but chewing sugarless gum after surgery[43] and early introduction of enteral nutrition after rectal surgery have been associated with a significant reduction in the time to return of bowel function[44].

Kim *et al.*[45] defined early postoperative small bowel obstruction (SBO), which differs from the POI in that it occurs secondary to early adhesions, lasting less than 7 days and usually resolved conservatively. In a systematic review of postoperative complications after colorectal surgery, early postoperative SBO was the second commonest cause of reoperation, which can be managed with a laparoscopic approach[30]. Often, the cause of intestinal obstruction is adhesions or an internal hernia[8].

Cardio-respiratory complications and other conditions

Cardiopulmonary dysfunction has been described in 4% of patients who underwent anterior resection. Chest infection incidence after LAR is 3.4%-10%[1,18], being slightly higher after LAR in comparison to open surgery due to greater operating time. Incidence of deep venous thrombosis has decreased considerably, with universal adoption of pneumatic calf compression devices, and the use of low molecular weight heparin extended up to 30 days postoperatively according to the European Society of Medical Oncology[46]. Another minor early complication associated with anterior resection is urinary retention, requiring temporary catheterization, following failed trial of voiding.

LONG-TERM COMPLICATIONS

Long-term morbidities are those that take place between the 30th post-operative day to 3 years following LAR[47].

Low anterior resection syndrome

Sphincter-preserving procedures with a low colorectal or coloanal anastomosis are associated with bowel dysfunction, which negatively affects the patient's quality of life (QOL). It may be multifactorial, including diminished rectal compliance, autonomic neuropraxia or neuropathy and impairment of internal anal sphincter tone[48]. Low anterior resection syndrome (LARS) is defined by high frequency of bowel movements, clustering, incomplete evacuation, diarrhoea, incontinence for flatus and stool, urgency, and bowel movements at night[49]. The severity of LARS can be measured with LARS score, a five-item instrument giving a score from 0 to 42. A range from 30 to 42 on the LARS questionnaire indicates major LARS, from 21 to 29 minor LARS, whereas scores below 21 can rule out LARS[50]. Unfortunately, its incidence is underestimated and its impact under-appreciated, as a recent survey among colorectal surgeons of different countries shows[51]. LARS is present in 55.2%-58% of patients who undergo low LAR[49,52], being more frequent after a low anastomosis and in young patients who received neoadjuvant chemoradiotherapy[52].

Management of LARS is quite challenging because of a dearth of successful treatment options. Conservative management consists of dietary adjustment adhering to a low fibre diet, antidiarrheal treatment, pelvic floor rehabilitation, biofeedback and colonic irrigation[49,51]. Some authors have suggested the use of sacral nerve stimulation after the failure of conservative management, with a success rate of 75% after a median follow up of 18 months, but its use has been described only in a small series of patients[49,53]. Further prospective studies are required to assess the success of this technique.

Incisional and port-side hernia

Laparoscopic approaches have reduced the incidence of incisional hernia, in 2.3%[54] to 13%[2] depending on the length of follow-up, but many rectal resections still require an abdominal incision for specimen extraction. A multivariate analysis performed by DeSouza *et al.*[55] identified high body-mass index, wound infection and diabetes as risk factors for incisional hernia, and the Pfannenstiel incision as independent protector of an incisional hernia. Many surgeons now choose to avoid a midline extraction site to minimize this complication. In a review of patients undergoing laparoscopic colorectal surgery, midline incisional hernia accounted for 84% of all hernias compared to 4.8% for Pfannenstiel incision[54]. However, authors report no benefit in extending the left iliac fossa port (transverse incision) rather than a midline incision, with similar incidence of extraction site incisional hernia and wound infection rate[56]. In order to avoid the risk of incisional hernias, some authors suggest the use of prophylactic mesh. A randomized controlled trial with patients undergoing colorectal surgery through a midline incision shows a reduction of incisional hernia in the group with a prophylactic overlay large-pore polypropylene mesh by 20.2%, without increase of SSIs with no mesh rejection[57].

Rectovaginal and colovesical fistulas

Rectovaginal fistula (RVF) is thought to be an infrequent complication after LAR, approximately 3%, appearing as a late complication, sometimes more than 3 months after surgery[58]. Clinical suspicion is confirmed by rectal and gynaecological examination, and by endoscopic and radiological investigations. Traditionally, previous hysterectomy and the experience of a surgeon using the circular stapler were described as prognostic factors of a RVF. Careful dissection between the rectal stump and posterior vaginal wall is required and a marked posterior angle introducing the circular stapler in the rectal stump, in order to avoid the inclusion of vaginal wall in the tissue rings (doughnuts)[59]. Other authors suggest malnutrition, neoadjuvant chemotherapy, tumour size ≥ 50 mm, intraoperative bleeding and lateral lymph node dissection as risk factors for developing RVF[58]. The American Society of Colon and Rectal Surgeons recommends delaying surgical intervention for a period of 3 to 6 months to allow possible spontaneous healing of the fistula; in the event of acute inflammation, a draining seton may be required[60]. There is no consensus regarding the need for faecal diversion but in some cases, diversion alone may result in healing[60,61]. RVF after anterior resection are typically too high to be repaired with a perineal approach and often requires an abdominal approach, to redo the anastomosis with omentoplasty interposed between the vagina and the rectum. In refractories RVF, a proctectomy with colon pull-through provides good results, with the caveat that functional outcome is suboptimal[61].

Some authors suggest that the persistence of an AL, even when there is a discrete sinus (1%-5% of LAR) could be associated to a rectovaginal/rectourethral/colovesical fistula, or also to some degree of stenosis, recommending early repair of AL in order to avoid these complications[28]. Urinary sepsis and the presence of gas in the bladder in absence of catheterisation raise suspicion of colovesical fistula [Figure 2].

Urinary and sexual dysfunction

Autonomic nerves can be damaged during total mesorectal excision. Dissection along the avascular plane between presacral fascia and mesorectal fascia, the so called "holy plane", preserves sacral vessels and autonomic nerves including the superior hypogastric plexus, the hypogastric nerves, the pelvic (inferior hypogastric) plexus, the pelvic splanchnic nerves, and the neurovascular bundle of Walsh[52]. However, the presence of urinary and sexual dysfunction among patients who underwent an anterior resection, as

Figure 2. Colovesical fistula in a patient undergoing laparoscopic anterior resection. Air in the bladder in the absence of catheterisation

a result of thermal and/or ischemic injury, tension or local inflammatory damage of autonomic nerves is well recognised[62]. Special attention must be paid during dissection at the origin of the inferior mesenteric artery, during the posterior mobilization of the rectum and lateral and anterior dissection of the rectum to minimise risk of nerve injury[63].

Due to sympathetic and parasympathetic nerve damage, patients describe incomplete urination, frequency of urination, interrupted urination, incontinence and low-flow urination. Urinary dysfunction may be easily evaluated with the International Prostate Symptom Score, which includes assessment of urinary symptoms and patient's QOL. Utilizing this scoring system, data suggest 12.7% of patients suffer from severe dysfunction after rectal resection[62].

For appropriate diagnosis and follow-up of urogenital dysfunction, The International Index of Erectile Function form for men and the International Index of Female Sexual Function for women are valuable and validated instruments to assess sexual dysfunction[63]. Some studies have reported impotence in 20%-46% and ejaculatory disorders in 20%-60% of men, whereas in women symptoms include loss of libido, vaginal moisture loss, orgasm loss and dyspareunia, being reported by 30% to 65% of patients after LAR[62,63]. Damage of superior hypogastric plexus and hypogastric nerves causes bladder instability (loss of relaxation) and retrograde ejaculation or loss of ejaculation in men, whereas damage of inferior hypogastric plexus leads to difficulties in bladder emptying and impotence[63].

Stoma complications

Stoma complications could be associated with significant morbidity, which is highest in the first 5 years postoperatively[64]. Some complications appear early in the postoperative course, such as fluid and electrolyte imbalance, peristomal dermatitis or stoma retraction because the bowel is under tension, often requiring stoma refashioning.

Parastomal hernias

There is a wide range of incidence of parastomal hernia, depending on the follow-up and the type of stoma. An incidence of 6.2% has been described for loop ileostomies, while the incidence is higher for colostomies depending on whether a hernia is diagnosed clinically (48.1%) or radiologically (80%)[65]. The fact that many ileostomies are temporary may lead to less incidence of long-term herniation[65]. Risk factors for the development of parastomal hernia are obesity, raised intra-abdominal pressure (chronic constipation, ascites, chronic cough), corticosteroid use, increased age, wound sepsis[66-69], malnutrition, smoking[69], diameter of the trephine and its location and emergency surgery without preoperative assessment by a stoma therapist[66].

Current treatment options include non-operative management, if the parastomal hernia is asymptomatic or stoma relocation and repair of the fascial defect with or without mesh. Primary fascial repair has been associated with high recurrence, from 50% to 75%[66,69]. Despite the fact that fewer recurrences are described with stoma relocation on the other side of the abdomen wall, there is a significant risk of an incisional hernia at the site of the original stoma and in addition, this technique could be limited if there are multiple previous surgeries[65]. The repair of fascial defect with mesh has been widely described with different techniques, placing the mesh on the top of the fascia of the rectus sheath (onlay), between the rectus abdominis muscle and posterior rectus sheath (sublay), and intraabdominal (underlay), fixed on to the peritoneum, which could be by open or laparoscopic approach. The onlay technique consists in the insertion of a polypropylene ring mesh around the stoma, avoiding a laparotomy, which may be convenient in high-risk patients. However, there is a high risk of recurrence and the infection rate is quite significant, 12.5%[66], requiring the removal of the mesh. The sublay mesh technique and the underlay mesh technique have been associated with less recurrence compared to the onlay technique, likely because the mesh is placed on the high-pressure side of the abdominal wall[69]. Unfortunately, there are minimal long-term data on the effectiveness of sublay mesh technique. The two most popular underlay techniques are the slit mesh Keyhole technique and the Sugarbaker technique. Both involve hernia sac reduction, adhesiolysis, and appropriate mesh fixation. The Sugarbaker approach involves the bowel being exteriorized through the side of the mesh creating a tunnel between the abdominal wall and the prosthesis, in the Keyhole approach the bowel is inserted through a hole placed in the centre of the mesh. The Sugarbaker technique was modified from the original version to prevent recurrent hernias, and an overlap of 3-5 cm between the mesh and the adjacent fascia around the trephine opening is now mandatory[70]. The largest Sugarbaker and Keyhole cohorts are published by Hansson *et al.*[71] in two different studies describing a recurrence of 37% after the Keyhole technique[71] compared to a recurrence rate of 6.6% in the group of Sugarbaker technique[70]. Authors justify these results because the mesh material used, polytetrafluoroethylene (ePTFE), has a tendency to shrink, which widens the slit in the mesh and consequently results in a hernia recurrence. DeAsis *et al.*[68] found also better results for the Sugarbaker technique but with a not insignificant risk of recurrence of 10.2%. Expanded ePTFE meshes are the most common prostheses described in the literature to deal with laparoscopic intraperitoneal hernia repair because there is less risk of adhesions to the bowel[68,70] compared to polypropylene mesh. However, the hydrophobicity of ePTFE and the lack of ingrowth of fibrocollagenous tissue into the prosthesis make it vulnerable to infection, so it is mandatory to avoid the use of mesh in a contaminated field[71]. Some authors have suggested the use of hybrid mesh types, with an inert mesh material such as polyvinylidene fluoride with a small amount of polypropylene on the parietal side, inducing ingrowth and incorporation[72].

In order to prevent a parastomal hernia, some groups have suggested the use of mesh placed prophylactically in the sublay position at the time of stoma creation[73]. A recent metanalysis of 10 randomized trials, analysing 649 patients in total, found that mesh reduced the rate of parastomal hernia repair by 65%, with a low rate of infection[74]. Nevertheless, the use of prophylactic mesh is still controversial and there is no clear consensus regarding it's use[66].

Other stoma complications

Stoma prolapse is defined as bowel intussusception, which protrudes through the stomal orifice [Figure 3]. Traditionally it has been described the use of sugar for helping in the manual reduction because it benefits

Figure 3. Prolapsed stoma

the exchange of fluids related to the osmotic gradient[64]. If there is any evidence of ischaemia, stoma should be refashioned.

Stomal stenosis is reported in 2%-15% of the stomas, and the commonest symptom is a noisy stoma when flatus is passed[64]. Management of this complication includes dilatations with Hagar's dilators and when it is not possible, surgical review of the stoma is recommended. Retraction of the stoma due to insufficient length of bowel, may be managed using convex appliance[75].

CONCLUSION

Laparoscopic rectal cancer surgery is safe, in the hands of fellowship-trained specialist surgeons. Morbidity and mortality can be minimised by the early recognition of complications and involvement of the multi-disciplinary team in management of such complications. Minimally invasive approaches are favoured by patients, and increasingly by surgeons, but the incidence and gravity of complications after laparoscopic rectal cancer surgery remain equivalent to traditional open surgery.

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Authors' contributions

Design, literature research, data analysis, manuscript writing, manuscript editing, manuscript revision: Climent M, Martin ST

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Manuscript Type	**Definition**	**Abstract**	**Keywords**	**Main Text Structure**
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Commentary	A Commentary is to provide comments on a newly published article or an alternative viewpoint on a certain topic.	Unstructured abstract. No more than 250 words.	3-8 keywords	/
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