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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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REVIEW

Pre-operative clinical and instrumental factors as antireflux surgery outcome predictors

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Abstract

Gastroesophageal reflux disease (GERD) is nowadays a highly prevalent, chronic condition, with 10% to 30% of Western populations affected by weekly symptoms. Many patients with mild reflux symptoms are treated adequately with lifestyle modifications, dietary changes, and low-dose proton pump inhibitors (PPIs). For those with refractory GERD poorly controlled with daily PPIs, numerous treatment options exist. Fundoplication is currently the most commonly performed antireflux operation for management of GERD. Outcomes described in current literature following laparoscopic fundoplication indicate that it is highly effective for treatment of GERD; early clinical studies demonstrate relief of symptoms in approximately 85%-90% of patients. However it is still unclear which factors, clinical or instrumental, are able to predict a good outcome after surgery. Virtually all demographic, esophagogastric junction anatomic conditions, as well as instrumental (such as presence of esophagitis at endoscopy, or motility patterns determined by esophageal high resolution manometry or reflux patterns determined by means of pH/impedance-pH monitoring) and clinical features (such as typical or atypical symptoms presence) of patients undergoing laparoscopic fundoplication for GERD can be factors associated with symptomatic relief. With this in mind, we sought to review studies that identified the factors that predict outcome after laparoscopic total

fundoplication.

Key words: Gastroesophageal reflux disease; Antireflux surgery; Outcome predictors; Fundoplication; Nissen; Laparoscopy; High resolution manometry; Impedance-pH monitoring

Core tip: Fundoplication is currently the most commonly performed antireflux operation for management of gastroesophageal reflux disease (GERD). Outcomes described in current literature following laparoscopic fundoplication indicate that it is highly effective for treatment of GERD. However it is still unclear which factors, clinical or instrumental, are able to predict a good outcome after surgery. Anatomical conditions seem to not be a risk factor for poor outcome. The predictability of success following laparoscopic fundoplication seems to be directly proportional to the degree of certainty that gastroesophageal reflux is the underlying cause of the patient's complaints. Thus, performing an accurate pre-operative clinical and instrumental evaluation is mandatory.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is currently a common condition; usually 10% to 30% of Western populations refer a weekly incidence of GERD symptoms. It has been recognized as a significant public health concern in the West[1,2]. Usually, the major part of patients with mild GERD are treated effectively with dietary and lifestyle changes, and/or low-dosage proton pump inhibitors (PPIs)[3]. For patients with GERD refractory to PPIs, different treatments can be started. In factantireflux surgery, and endoscopic procedures exist for patients who will to undergo an operative intervention. Fundoplication is currently considered the surgical gold standard for GERD treatment. Since its first description by Rudolph Nissen in 1956[4], the development of laparoscopy have increased the use of fundoplication worldwide. The indications for antireflux surgery in GERD patients were stated by the American Gastroenterological Association in 2013: It can be indicated in a GERD patient responsive, but not compliant to acid suppression therapy; in GERD patients who continue to experience troublesome symptoms despite an adequate pharmacological therapy; and in GERD patient who experience persistent extraesophageal symptoms despite adequate PPI therapy[5].

LF outcomes (as reported in current literature) point out that this technique is highly effective in GERD patients; the relief of symptoms is present in 85%-90% of subjects in the immediate post-operative period[6,7]. Despite these encouraging data, there can be complications that can necessitate a second intervention: Re-herniation, disruption or twisting of the fundoplication, persistent dysphagia or reflux-related symptoms, gas bloat syndrome, and esophageal motor disfunction[8,9]. Also, it is not clear the real incidence of redo antireflux surgery, because of small sample size or are single center studies. In the 90's, Lafullarde reported an overall reoperation rate of 10% after LF[10]. More recently, reoperation incidence is reported to be resembling 5%[11]. A systematic review performed on elective LF documented an overall reoperation incidence approximating 0.6%[12]. In the nationwide study from Denmark, an incidence near to 5% of redo antireflux surgery was reported in 2589 patients[13].

Being the increasing number of GERD patients without endoscopic esophagitis that are selected for LF, there is the need to highlight the great significance of a careful selection of patients who are likely to have a successful outcome after surgery. Virtually all demographic, esophagogastric junction anatomic conditions, as well as instrumental and clinical features of patients undergoing LF for GERD can be factors associated with a good outcome. With this in mind, we sought to review studies that identified the factors that could predict outcome after LF.

DEMOGRAPHICS FACTORS (GENDER, AGE, OBESITY, COMORBIDITIES)

Some studies revealed that gender can affect the clinical manifestation of GERD. Female gender with GERD showed at pH-monitoring a minor value of esophageal acid exposure and greater symptom scores than male gender cross-matched for grades of esophagitis[14,15]. In the same way, age seems to influence presentation, and GERD-related symptoms usually appear less severe in elderly, with a greater incidence of reflux complications[16]. In 2009, a study investigated the impact of gender and age on 5 years outcome of LF[17]. Authors showed that women were more likely to report a poorer outcome than men, describing heartburn, dysphagia and a lower satisfaction rate after surgery. Age, instead, did not prejudiced surgical outcome, even in presence of an higher incidence of complicated esophagitis and acid exposure in elderly than younger subjects[18]. These results were also confirmed by two large case series from Italy that compared antireflux surgical outcome in patients younger or older than 65 years[19,20]. Overweight and obesity are associated

with increased intraabdominal pressure, presence of hiatal hernia, increased frequency of transient sphincter relaxation , diminished lower esophageal sphincter (LES) pressure, and and impaired gastric emptying, thus increasing esophageal acid exposure time (AET) and total number of reflux (TNR), which have a clear role in GERD and promoting symptoms[21,22]. Recently, Luketina *et al*[23] retrospectively evaluated antireflux surgical outcomes in obese patients compared to normal weight GERD patients. Body mass index (BMI) was not associated to poorer outcome; reduction in GERD symptom score, GERD recurrence and reoperation rates were similar in both obese and normal weight patients. These data are consistent to several case-series[24,25], whereas only few studies reported poorer outcomes after LF in obese subjects, with increased intraoperative difficulties, risk of recurrence and re-herniation[26]. Finally, a study performed on a large cohort from North Carolina suggested that presence of pre-operative comorbities, such as diabetes, hypertension or pulmonary disease, were unlikely to impair the outcome of LF[27].

CLINICAL FACTORS: SYMPTOMS

Clinical presentation of GERD patients varies from typical to atypical symptoms, as well as extraesophageal symptoms and associated syndromes.

Heartburn and regurgitation are considered the hallmarks of reflux disease. Atypical reflux symptoms include non-cardiac chest pain and extraesophageal manifestations such as chronic cough, chronic asthma, chronic laryngitis, and dental erosions. Also, dyspepsia manifestations and irritable bowel syndrome symptoms can be present in up to 50% of GERD patients[28].

Many studies were performed to verify the post-operative symptomatic gain after LF, in order to estimate its clinical effectiveness. Morgenthal *et al*[29] studied a cohort of 166 subjects with 11 years follow-up of; authors showed that typical symptoms presence was a predictive factor for a long term good outcome after LF. Lundell *et al*[30] performed a systematic review about the outcome of antireflux surgery. They found that patients did not experience heartburn substantially in the year after LF but it reappeared over time, with a certain amount of patients reporting heartburn after 10 years. Similarly, patients reporting regurgitation reported a substantial reliefin the year after LF but with a recurrence 10 years after LF[30].

Achieving atypical GERD symptoms response is challenging: In a recent review, authors did not find any sure data on the efficacy of LF in relieving these manifestations, even if the majority of studies demonstrated some degree of improvement[31]. However, when a patient is selected on the basis of pH-impedance monitoring, LF showed a significant relief of extraesophageal symptoms but it seems to cannot improve all of the patients. Adaba *et al*[32] studied respiratory symptoms in patients with GERD and then treated with LF. They stratified the study population into three groups; patients with cough only, patients with cough plus other respiratory symptoms (asthma, COPD, bronchitis, interstitial lung disease and hoarseness of voice) and patients with other respiratory symptoms only. Patients with cough only were likely to have a better symptoms improvement than patients with cough plus respiratory symptoms and respiratory symptoms only in the short and long term, even if the small number of patients represented a limitation. This trend has also been observed in other studies[33,34]. Overall response rates were over 70% in the control of respiratory manifestations. A recent review speculated that cough and reflux may stimulate each other[35]. Cough showed the highest preoperative scores than all extraesophageal manifestations and was referred by about 45% of the subjects.

Finally, the presence of dyspepsia-like symptoms seems to be a negative factor for outcome. In fact, several studies reported that after surgery there are subjects who will get worse or exacerbate dyspepsia-like symptoms (epigastric fullness, bloating, abdominal pain, flatulence), with worsening in GERD symptom control in up to 50% at long term follow-up[36,37].

CLINICAL FACTORS: RESPONSE TO PPI

Acid-suppression with PPIs is the most widespread used therapy for GERD. Actually, patients who control their symptoms and resolve mucosal lesions with PPIs are referred to as "complete responders", whereas "partial responders" or "non-responders" are those increasingly numbers of patients experiencing only partial or no relief from reflux symptoms, even after optimized PPI[38]. The LF is currently contemplated in patients with hiatus hernia and, according to some surgeons, in patients non-responsive to PPI[39], whereas other surgeons do not consider the surgical treatment as a good option in PPI non-responders.

Several studies evaluated the clinical effectiveness of surgical treatment of GERD in PPI responders and nonresponders. According to Lundell *et al*[30], partial responders were the ones needing to use acid-suppressive medication and requiring surgical reintervention after LF. These results are consistent with a recent study; authors in fact showed that the pre-operative symptomatic response to PPI treatment was an excellent predictor of the subsequent response to LF[40]. In Campos *et al*[41] performed a multivariate analysis, demonstrating that pre-operative PPI refractoriness was a predictive factor of poor outcome after LF. In fact, PPI non-responders patients had a significantly effectiveness from the surgical treatment but it was still less successful when matched with PPI responders. Also, other studies considered the surgical outcome in non-responders, evaluating those also affected by atypical symptoms, reflecting that surgical procedure can be uneffective to treat atypical symptoms. Hamdy et coll, therefore, realized a prospective study on patients

responders and non-responders who underwent LF[42]. The two groups were matched for endoscopic grading of esophagitis as well as no significant difference between the two groups on functional assessment on esophageal manometric study of LES pressure and pH-monitoring. According to their findings, clinical outcome was better in PPIs responders regarding disappearance of heartburn and regurgitation, while there was no difference in improvement of dysphagia between both groups. Also, overall patient satisfaction with surgery was significantly higher in the good responders. Authors concluded that patients responder to PPI have a positive predictive factor for LF outcome, whereas PPI non responders are not at risk for a contraindication. However, PPI non-responders have experienced the failure of the pharmacological therapy, evaluating the surgical treatment as the last opportunity for their relief. So that, surgeons and gastroenterologists should accurately and carefully select patients non-responders to maximize LF outcomes: PPI non responders and/or patients complaining atypical digestive symptoms should avoid a surgical procedure to treat GERD, if the real presence of GERD and a possible symptom-reflux correlation is not documented.

ANATOMICAL FACTORS: HIATAL HERNIA PRESENCE

Mechanisms of GERD are multifactorial (dysfunction of esophageal peristalsis, gastric activity, and LES continence). The presence of hiatal hernia exposes patients to increased AET, TNR and to a more severe GERD pattern[43]. In literature in fact, is currently reported that at baseline hiatus hernia, LES resting pressure and length are significantly more compromised in patients with severe erosive reflux disease (ERD) and Barrett's esophagus (BE) compared to those with mild erosions and non erosive reflux disease (NERD).

Intuitively, GERD patients with a normal LES pressure at manometry would have less acid reflux and related symptoms at baseline; thus, they could be more likely to experience dysphagia after LF, with generally worse outcomes. On the other hand, hiatal hernia is often found in patients reporting dissatisfaction and/or undergoing reoperativeantireflux surgery. Its persistence after LF is in fact a predictive factor of negative outcome[44].

Lord *et al*[45] demonstrated not only that the grade of GERD well links with the functional and anatomical qualities of the gastroesophageal reflux barrier, with hiatus hernia, and that a defective LES is significantly more frequent in ERD or BE patients, but also that LF, which resolves the hernia and increases the LES pressure, offers in the same way good or excellent outcomes, irrespective of the presence of mucosal inflammation, and in all degrees of GERD[45]. Similarly, Lei *et al*[46] study the effect of LF in treating sliding hiatal hernia. They found that at 2 years follow-up in up to 93% of subjects a normal instrumental testing was present, with a good overall satisfaction. Cowgill *et al*[47] compared a group of patients with GERD that had a normal LES resting pressure, to a group of patients with inadequate LES, before and after LF was performed. They found that before surgery, patients with normal LES tone had symptom scores (for heartburn and regurgitation) similar to those patients with inadequate LES, and the symptom relief was also similar after LF. Inability to belch was not frequent at baseline, and its presence did not increased postoperatively. Furthermore, dysphagia scores significantly improved in patients, irrespective for inadequate and adequate LES pressure, whereas dysphagia frequency did not improve in those adequate or inadequate LES pressure at manometry.

ENDOSCOPIC FACTORS: ESOPHAGITIS, NERD AND BE

Deterioration of esophageal clearance function protracts contact of the refluxate, thus increasing mucosal damage, that can be documented during endoscopy. Therefore, GERD patients may present with a broad spectrum of endoscopic mucosal presentation (normal to esophagitis to BE).

However, a the majority of patients complaining GERD symptoms have no mucosal lesions at endoscopical imaging[48,49], while in others gastric acid reflux may trigger ERD and causing a weakening of esophageal peristalsis[50]. It could be expected that GERD patients without esophagitis suffer of a less symptomatic disease, and that the presence or absence of esophagitis at the endoscopic exam, could somehow influence the management of those patients, expecting that NERD patients could be treated with medical therapy whereas patients with esophagitis would need other approaches instead. Additionally, it could be thought that NERD subjects would have superior perioperative outcomes than ERD patients, but having less favorable long-term outcomes when compared to the ERDs.

Recently, there are confirmation that NERD subjects are similar to ERDs for reflux patterns, symptoms severity, and use of medical therapy[51].

Additionally, recent reports advocate that a less aggressive therapy (cisapride, anti-H2) in NERD subjects is often ineffective, and they necessitate high-dose PPI; also, they experience relapse frequently, and a lower response rates to omeprazole when compared to ERDs[52,53]. For these reasons, management strategies for NERD should be based on the same principles as those for ERD.

Lots of studies were taken to evaluate preoperative influence of esophagitis in GERD patients, and to evaluate how the presence of erosions would affect the outcome of surgery. The hypotheses that NERD patients would have better perioperative results with less

favorable long-term outcome than ERD is false. LF is an efficient treatment for GERD, with no significant clinical differences between patients with and without ERD at baseline. For patients with NERD, LF offers significant relief of symptoms and a marked diminution in the use of PPI[54].

Some investigators reported relatively poorer outcomes of LF for patients with BE and suggested the use of more aggressive surgical strategies for BE developed in GERD patients[55]. However, a study from Cowgill *et al*[56] compared patients with GERD with or without BE to verify the presence of differences in symptoms relative frequency and severity and in relative levels of acid reflux preoperatively and to verify symptom improvement postoperatively. Authors postulated that patients with BE would experience more severe reflux and symptoms at baseline, with poorer effects after LF than patients without BE. However, before surgery, even if BE patients showed higher DeMeester scores, symptom scores were not significantly different than patients without BE. After LF, symptoms scores improved for both group of patients. After LF, all symptoms scores significantly improved, whereas dysphagia frequency was higher in patients with BE. Similarly, Abbas *et al*[57] noticed that 67% of 49 BE patients after LF were asymptomatic at follow-up. Also, Oelschlager *et al*[58] reported excellent outcomes in GERD and BE patients, with up to 95% of the subjects reporting a persistent symptomatic improvement after LF. Tolone *et al*[59] showed optimal reflux control in BE patients after LF, documenting it by the means of MII-pH monitoring; also Authors showed regression of low grade dysplasia one year after surgery.

INSTRUMENTAL FEATURES: MOTILITY

Esophageal dysmotility commonly occurs with GERD. In the study by Savarino *et al*[60], which combined esophageal manometry and impedance, patients with reflux esophagitis have been shown to have a significant increase in esophageal motility and bolus transit abnormalities compared to healthy controls and patients with NERD. Although the association between GERD and esophageal dysmotility is clear, GERD symptoms relief after medical therapy is not proven to be helpful in improving esophageal motility. In fact, although PPIs are able to fully resolve reflux esophagitis and are successful in the majority of patients in terms of symptom relief, it has been shown that they have no effect on the improvement of esophageal body motility[61]. On the other hand, the surgical correction of GERD offers an improvement or a complete resolution of esophageal dysmotility[62]. However, medical good-sense purposes a limited role for LF if esophageal dysmotility is present, fearing for postoperative dysphagia development. Coherently, successful results after LF in patients with esophageal motor dysfunction are not easy to predict[63]. Various studies considered ineffective esophageal motility not to be a risk factor for prolonged postoperative dysphagia after LF[64,65]. Even if several studies reported excellent outcomes after LF in patients with manometric motor disorders, these results are not entirely shared. Dysphagia can observed in a considerable amount (up to 20%) of GERD patients and esophageal motor abnormalities after LF[66,67].

The study conducted from D'Alessio *et al*[68], showed that patients with esophageal motor dysfunction determined at manometry had adequate outcomes after LF if they were able to effectively clear a food bolus at preoperative esophagography. These patients had similar outcomes to those with normal esophageal motor function. Pizza *et al*[69], studied different patients divided into groups according to the motility pattern studied preoperatively with manometry. They divided a group A with impaired esophageal peristalsis, and group B without impaired peristalsis. Their study demonstrated that the two groups had a statistically significant improvement in symptom score and that preoperative defective esophageal peristalsis was not a contraindication to LF.

Another aspect to be considered is the preoperative LES resting pressure at manometry, because experience with LF in GERD patients and manometrically intact LES is limited. In the majority of GERD subjects an impaired LES competence is documented at esophageal manometry, thus reflux presence is easily argued. In those with manometrically adequate LES, several other mechanisms (transient involuntary relaxations of the LES, impaired esophageal peristalsis, decreased gastric emptying, increased intragastric or intraabdominal pressure, increased BMI, life-style habits) have been proposed to explain the occurrence of GERD.

Riedl *et al*[70] studied the importance of LES pressure and its hypothetic capacity to influence the outcome of LF when a normal pressure was present. In their study, they stratified 4 groups: Group Ⅰ (LES with a defective intra-abdominal length and a defective pressure), group Ⅱ (defective LES pressure), group Ⅲ (defective LES intra-abdominal length), and group Ⅳ (normal LES). They found no significant differences among the groups regarding the quality of GERD symptoms and quality of life scores. Similar conclusions led the study of Patti *et al*[71] where authors studied three groups based on the preoperative LES pressure. The resolution of symptoms and incidence in the novo dysphagia was similar among the three groups, irrespective of the preoperative LES status. Also, authors found that LF was linked to a higher percentage of postoperative dysphagia than partial fundoplication, regardless the LES pressure at baseline.

Finally, a new parameter at high resolution manometry, the esophagogastric junction contractile integral, was recently used to better prove the antireflux barrier efficacy of the junction[72]. The group from St Louis showed that this metric distinguished patients with normal AET from those with pathological values better than conventional LES parameters, and that it can be useful to evaluate the efficacy of the anti-reflux

surgery[73].

INSTRUMENTAL FEATURES: ESOPHAGEAL ACID EXPOSURE

Outstandingly, GERD patients are really a heterogeneous population. By means of 24-h ambulatory esophageal pH monitoring, AET can be quantified and qualified depending on the body position in which it appears. According this latter feature, three reflux patterns of acid reflux at pH-monitoring are usually reported: Unique upright, unique supine, and bipositional one. The presence of abnormal supine and bipositional AET are considered classic indication for antireflux surgery[74]. However, some investigators believe that symptom improvement and success after LF could depend upon the AET-body position pattern. It is reasonable to accept that LF outcomes can vary according to the reflux patterns. Upright reflux, for example, is cogitated to be a less severe GERD pattern, whereas bipositional reflux seems to be associated with advanced, severe disease. Although upright reflux is considered an initial form of GERD, these subjects are supposed to present a greater incidence of aerophagia and dyspepsia. Also, these patients are supposed to have worse postoperative outcomes after LF, including higher rates of postoperative gas bloating and flatus, when compared to those with supine or bipositional pathological AET[75,76]. Consequently, some physicians have been hesitant to indicate LF in presence of isolated upright pathological AET[77].

However, several papers are even in contrast on this matter. In fact, different studies found a similar symptoms relief in patients with pathological upright reflux and in those with pathological supine or bipositional AET[78,79]. Only two studies evaluated objectively the outcomes of LF and demonstrated that isolated upright reflux patients had a good outcome after surgical intervention[80,81]. Other authors have recently reopened the debate and it has been reported that poorer symptomaticimprovement occurs after surgery in patients with pathological upright reflux[82]. Cowgill *et al*[83] studied a large cohort of GERD patients who required antireflux surgery. Authors stratified patients according to positional AET features at baseline pH-monitoring. Patient with reflux occurring in any position, even in only upright reflux, experienced similar good symptom improvement after LF; in fact, a larger percentage of patients with upright reflux defined their overall outcomes as "excellent" or "good". All symptoms improved postoperatively. Authors concluded that after LF, symptoms of GERD improved in all reflux patterns and that LF dramatically improves GERD symptoms, irrespectively of the reflux pattern; thus, antireflux surgery is encouraged. Actually, it remains debated whether upright reflux should be considered as a relative contraindication for LF, because studies comparing long-term objective and subjective parameters are lacking.

INSTRUMENTAL FEATURES: IMPEDANCE-PH MONITORING

Combined multichannel intraluminal impedance-pH (MII–pH) monitoring can identify reflux events independently of its pH quality. In recent years, in fact, MII-pH monitoring has become a progressively adopted method in the evaluation of GERD. Because MII-pH monitoring detects retrograde movements in the esophagus regardless of an acid pH drop, it permits to document either nonacid or weakly acidic reflux events (with a pH higher than 4). This central advantage allows to evaluate GERD patients with refractory symptoms during acid-suppression therapy; in fact, recent studies have shown the capacity of MII-pH monitoring in increasing the symptom index sensitivity for patients on PPIs[84,85].

Mainie *et al*[86] assessed LF as a management for patients with PPI refractory symptoms associated with reflux, by means of MII-pH monitoring. Authors found that at baseline 18 of 19 patients had a positive symptom index and one, a negative symptom index. At postoperative follow-up (14 mo), 94% of patients with a positive symptom index were asymptomatic or with a marked improvement. Persistent symptoms were experienced in the patient with a negative symptom index, and one patient had recurrent symptoms after 9 mo. Authors concluded that patients resistant to PPI with a positive symptom index demonstrated by MII-pH monitoring could be managed successfully by LF.

Del Genio *et al*[87] in 2008 verified if the MII-pH was effective to provide a correct selection of patients for LF. Authors prospectively assessed and reviewed data from 314 consecutive patients not responsive or not compliant to PPI who underwent MII-pH for GERD. One hundred fifty-three patients who underwent LF with a minimum follow-up of 1 year were included in the study. Outcomes were reported for patients with normal and ineffective peristalsis and for patients with positive pH-monitoring, negative pH-monitoring and positive total number of reflux episodes at MII, and negative pH-monitoring and normal number of reflux episodes at MII and a positive symptom index correlation with MII (hypersensitive esophagus patients). The overall patient satisfaction rate after surgery was 98.3%. No differences in patients' satisfaction and clinical postoperative symptom score were recorded between the groups as stratified by MII-pH. Authors concluded that MII-pH provided a useful objective selection of patients for LF and that LF can provide excellent outcomes in either patients with positive pH or negative pH and positive MII monitoring or symptom index association. These results were later confirmed by another Italian group that documented the positive impact of LF on reflux control in patients who

underwent MII-pH before and after surgery[88].

CONCLUSION

The LF is a good and efficacy therapeutical option for GERD. However, due to great heterogeneity in the phenotypical appearance of GERD, it is arguable that the outcomes of LF can be affected by a great number of factors. Based on the results highlighted in literature, a correctly fashioned LF, and, more important, a correctly indication to LF can provide optimal results with good patient satisfaction. Thus, in large part, the predictability of success following LF is directly proportional to the level of certainty that GERD is the underlying cause of the patient's symptoms. Pre-operative testing are mandatory, especially MII-pH, due to its ability to better stratify GERD patients and to better identify the reflux-symptom association.

REFERENCES

1 **Dent J**, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710-717 [PMID: 15831922 DOI: 10.1136/gut.2004.051821]

2 **Hansen JM**, Wildner-Christensen M, Schaffalitzky de Muckadell OB. Gastroesophageal reflux symptoms in a Danish population: a prospective follow-up analysis of symptoms, quality of life, and health-care use. *Am J Gastroenterol* 2009; **104**: 2394-2403 [PMID: 19623171 DOI: 10.1038/ajg.2009.391]

3 **de Bortoli N**, Guidi G, Martinucci I, Savarino E, Imam H, Bertani L, Russo S, Franchi R, Macchia L, Furnari M, Ceccarelli L, Savarino V, Marchi S. Voluntary and controlled weight loss can reduce symptoms and proton pump inhibitor use and dosage in patients with gastroesophageal reflux disease: a comparative study. *Dis Esophagus* 2016; **29**: 197-204 [PMID: 25516110 DOI: 10.1111/dote.12319]

4 **NISSEN R**. A simple operation for control of reflux esophagitis. *Schweiz Med Wochenschr* 1956; **86**: 590-592 [PMID: 13337262]

5 **Katz PO**, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; **108**: 308-328; quiz 329 [PMID: 23419381 DOI: 10.1038/ajg.2012.444]

6 **Davis CS**, Baldea A, Johns JR, Joehl RJ, Fisichella PM. The evolution and long-term results of laparoscopic antireflux surgery for the treatment of gastroesophageal reflux disease. *JSLS* 2010; **14**: 332-341 [PMID: 21333184 DOI: 10.4293/108680810X12924466007007]

7 **Arguedas MR**, Heudebert GR, Klapow JC, Centor RM, Eloubeidi MA, Wilcox CM, Spechler SJ. Re-examination of the cost-effectiveness of surgical versus medical therapy in patients with gastroesophageal reflux disease: the value of long-term data collection. *Am J Gastroenterol* 2004; **99**: 1023-1028 [PMID: 15180720 DOI: 10.1111/j.1572-0241.2004.30891.x]

8 **Dallemagne B**, Arenas Sanchez M, Francart D, Perretta S, Weerts J, Markiewicz S, Jehaes C. Long-term results after laparoscopic reoperation for failed antireflux procedures. *Br J Surg* 2011; **98**: 1581-1587 [PMID: 21710482 DOI: 10.1002/bjs.7590]

9 **Horgan S**, Pohl D, Bogetti D, Eubanks T, Pellegrini C. Failed antireflux surgery: what have we learned from reoperations? *Arch Surg* 1999; **134**: 809-815; discussion 815-817 [PMID: 10443802 DOI: 10.1001/archsurg.134.8.809]

10 **Lafullarde T**, Watson DI, Jamieson GG, Myers JC, Game PA, Devitt PG. Laparoscopic Nissen fundoplication: five-year results and beyond. *Arch Surg* 2001; **136**: 180-184 [PMID: 11177138 DOI: 10.1001/archsurg.136.2.180]

11 **Byrne JP**, Smithers BM, Nathanson LK, Martin I, Ong HS, Gotley DC. Symptomatic and functional outcome after laparoscopic reoperation for failed antireflux surgery. *Br J Surg* 2005; **92**: 996-1001 [PMID: 15997449 DOI: 10.1002/bjs.4914]

12 **Mariette C**, Pessaux P. Ambulatory laparoscopic fundoplication for gastroesophageal reflux disease: a systematic review. *Surg Endosc* 2011; **25**: 2859-2864 [PMID: 21487865 DOI: 10.1007/s00464-011-1682-5]

13 **Funch-Jensen P**, Bendixen A, Iversen MG, Kehlet H. Complications and frequency of redo antireflux surgery in Denmark: a nationwide study, 1997-2005. *Surg Endosc* 2008; **22**: 627-630 [PMID: 18071800 DOI: 10.1007/s00464-007-9705-y]

14 **Banki F**, Demeester SR, Mason RJ, Campos G, Hagen JA, Peters JH, Bremner CG, Demeester TR. Barrett's esophagus in females: a comparative analysis of risk factors in females and males. *Am J Gastroenterol* 2005; **100**: 560-567 [PMID: 15743352 DOI: 10.1111/j.1572-0241.2005.40962.x]

15 **Lin M**, Gerson LB, Lascar R, Davila M, Triadafilopoulos G. Features of gastroesophageal reflux disease in women. *Am J Gastroenterol* 2004; **99**: 1442-1447 [PMID: 15307857 DOI: 10.1111/j.1572-0241.2004.04147.x]

16 **Cowgill SM**, Arnaoutakis D, Villadolid D, Al-Saadi S, Arnaoutakis D, Molloy DL, Thomas A, Rakita S, Rosemurgy A. Results after laparoscopic fundoplication: does age matter? *Am Surg* 2006; **72**: 778-783; discussion 783-784 [PMID: 16986386]

17 **Beck PE**, Watson DI, Devitt PG, Game PA, Jamieson GG. Impact of gender and age on the long-term outcome of laparoscopic fundoplication. *World J Surg* 2009; **33**: 2620-2626 [PMID: 19771470 DOI: 10.1007/s00268-009-0216-y]

18 **Zhu H**, Pace F, Sangaletti O, Bianchi Porro G. Features of symptomatic gastroesophageal reflux in elderly patients. *Scand J Gastroenterol* 1993; **28**: 235-238 [PMID: 8446848 DOI: 10.3109/00365529309096078]

19 **Pizza F**, Rossetti G, Limongelli P, Del Genio G, Maffettone V, Napolitano V, Brusciano L, Russo G, Tolone S, Di Martino M, Del Genio A. Influence of age on outcome of total laparoscopic fundoplication for gastroesophageal reflux disease. *World J Gastroenterol* 2007; **13**: 740-747 [PMID: 17278197]

20 **Tolone S**, Docimo G, Del Genio G, Brusciano L, Verde I, Gili S, Vitiello C, D'Alessandro A, Casalino G, Lucido F, Leone N, Pirozzi R, Ruggiero R, Docimo L. Long term quality of life after laparoscopic antireflux surgery for the elderly. *BMC Surg* 2013; **13** Suppl 2: S10 [PMID: 24267446 DOI: 10.1186/1471-2482-13-S2-S10]

21 **Tolone S**, Savarino E, de Bortoli N, Frazzoni M, Furnari M, d' Alessandro A, Ruggiero R, Docimo G, Brusciano L, Gili S, Pirozzi R, Parisi S, Colella C, Bondanese M, Pascotto B, Buonomo N, Savarino V, Docimo L. Esophagogastric junction morphology assessment by high resolution manometry in obese patients candidate to bariatric surgery. *Int J Surg* 2016; **28** Suppl 1: S109-S113 [PMID: 26718611 DOI: 10.1016/j.ijsu.2015.12.047]

22 **Tolone S**, Limongelli P, del Genio G, Brusciano L, Rossetti G, Amoroso V, Schettino P, Avellino M, Gili S, Docimo L. Gastroesophageal reflux disease and obesity: do we need to perform reflux testing in all candidates to bariatric surgery? *Int J Surg* 2014; **12** Suppl 1: S173-S177 [PMID: 24859401 DOI: 10.1016/j.ijsu.2014.05.016]

23 **Luketina RR**, Koch OO, Köhler G, Antoniou SA, Emmanuel K, Pointner R. Obesity does not affect the outcome of laparoscopic antireflux surgery. *Surg Endosc* 2015; **29**: 1327-1333 [PMID: 25294529 DOI: 10.1007/s00464-014-3842-x]

24 **Winslow ER**, Frisella MM, Soper NJ, Klingensmith ME. Obesity does not adversely affect the outcome of laparoscopic antireflux surgery (LARS). *Surg Endosc* 2003; **17**: 2003-2011 [PMID: 14577029 DOI: 10.1007/s00464-003-8118-9]

25 **Ng VV**, Booth MI, Stratford JJ, Jones L, Sohanpal J, Dehn TC. Laparoscopic anti-reflux surgery is effective in obese patients with gastro-oesophageal reflux disease. *Ann R Coll Surg Engl* 2007; **89**: 696-702 [PMID: 17959008 DOI: 10.1308/003588407X205323]

26 **Hahnloser D**, Schumacher M, Cavin R, Cosendey B, Petropoulos P. Risk factors for complications of laparoscopic Nissen fundoplication.

Surg Endosc 2002; **16**: 43-47 [PMID: 11961603 DOI: 10.1007/s004640090119]
27 **Varban OA**, McCoy TP, Westcott C. A comparison of pre-operative comorbidities and post-operative outcomes among patients undergoing laparoscopic nissen fundoplication at high- and low-volume centers. *J Gastrointest Surg* 2011; **15**: 1121-1127 [PMID: 21557016 DOI: 10.1007/s11605-011-1492-z]
28 **Frazzoni M**, Piccoli M, Conigliaro R, Frazzoni L, Melotti G. Laparoscopic fundoplication for gastroesophageal reflux disease. *World J Gastroenterol* 2014; **20**: 14272-14279 [PMID: 25339814 DOI: 10.3748/wjg.v20.i39.14272]
29 **Morgenthal CB**, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. *Surg Endosc* 2007; **21**: 1978-1984 [PMID: 17623236]
30 **Lundell L**, Bell M, Ruth M. Systematic review: laparoscopic fundoplication for gastroesophageal reflux disease in partial responders to proton pump inhibitors. *World J Gastroenterol* 2014; **20**: 804-813 [PMID: 24574753 DOI: 10.3748/wjg.v20.i3.804]
31 **Koch OO**, Antoniou SA, Kaindlstorfer A, Asche KU, Granderath FA, Pointner R. Effectiveness of laparoscopic total and partial fundoplication on extraesophageal manifestations of gastroesophageal reflux disease: a randomized study. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: 387-391 [PMID: 23047378 DOI: 10.1097/SLE.0b013e31825efb5b]
32 **Adaba F**, Ang CW, Perry A, Wadley MS, Robertson CS. Outcome of gastro-oesophageal reflux-related respiratory manifestations after laparoscopic fundoplication. *Int J Surg* 2014; **12**: 241-244 [PMID: 24463143 DOI: 10.1016/j.ijsu.2014.01.005]
33 **Allen CJ**, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax* 1998; **53**: 963-968 [PMID: 10193396 DOI: 10.1136/thx.53.11.963]
34 **Tolone S**, Del Genio G, Docimo G, Brusciano L, del Genio A, Docimo L. Objective outcomes of extra-esophageal symptoms following laparoscopic total fundoplication by means of combined multichannel intraluminal impedance pH-metry before and after surgery. *Updates Surg* 2012; **64**: 265-271 [PMID: 22875788 DOI: 10.1007/s13304-012-0171-2]
35 **Galmiche JP**, Zerbib F, Bruley des Varannes S. Review article: respiratory manifestations of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008; **27**: 449-464 [PMID: 18194498 DOI: 10.1111/j.1365-2036.2008.03611.x]
36 **Broeders JA**, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**: 698-706 [PMID: 19801931 DOI: 10.1097/SLA.0b013e3181bcdaa7]
37 **Broeders JA**, Draaisma WA, Bredenoord AJ, Smout AJ, Broeders IA, Gooszen HG. Impact of symptom-reflux association analysis on long-term outcome after Nissen fundoplication. *Br J Surg* 2011; **98**: 247-254 [PMID: 20960456 DOI: 10.1002/bjs.7296]
38 **Sifrim D**, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut* 2012; **61**: 1340-1354 [PMID: 22684483 DOI: 10.1136/gutjnl-2011-301897]
39 **Bais JE**, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC, van Lanschot JJ, Nadorp JH, Smout AJ, van der Graaf Y, Gooszen HG. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170-174 [PMID: 10675115 DOI: 10.1016/S0140-6736(99)03097-4]
40 **Kamolz T**, Granderath FA, Pointner R. The outcome of laparoscopic antireflux surgery in relation to patients' subjective degree of compliance with former antireflux medication. *Surg Laparosc Endosc Percutan Tech* 2003; **13**: 155-160 [PMID: 12819497 DOI: 10.1097/00129689-200306000-00003]
41 **Campos GM**, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S, DeMeester SR, Hagen JA, Bremner CG. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 1999; **3**: 292-300 [PMID: 10481122 DOI: 10.1016/S1091-255X(99)80071-7]
42 **Hamdy E**, El Nakeeb A, Hamed H, El Hemaly M, ElHak NG. Outcome of laparoscopic Nissen fundoplication for gastroesophageal reflux disease in non-responders to proton pump inhibitors. *J Gastrointest Surg* 2014; **18**: 1557-1562 [PMID: 24985244 DOI: 10.1007/s11605-014-2584-3]
43 **Tolone S**, de Cassan C, de Bortoli N, Roman S, Galeazzi F, Salvador R, Marabotto E, Furnari M, Zentilin P, Marchi S, Bardini R, Sturniolo GC, Savarino V, Savarino E. Esophagogastric junction morphology is associated with a positive impedance-pH monitoring in patients with GERD. *Neurogastroenterol Motil* 2015; **27**: 1175-1182 [PMID: 26010058 DOI: 10.1111/nmo.12606]
44 **Ohnmacht GA**, Deschamps C, Cassivi SD, Nichols FC, Allen MS, Schleck CD, Pairolero PC. Failed antireflux surgery: results after reoperation. *Ann Thorac Surg* 2006; **81**: 2050-2053; discussion 2053-2054 [PMID: 16731129 DOI: 10.1016/j.athoracsur.2006.01.019]
45 **Lord RV**, DeMeester SR, Peters JH, Hagen JA, Elyssnia D, Sheth CT, DeMeester TR. Hiatal hernia, lower esophageal sphincter incompetence, and effectiveness of Nissen fundoplication in the spectrum of gastroesophageal reflux disease. *J Gastrointest Surg* 2009; **13**: 602-610 [PMID: 19050984 DOI: 10.1007/s11605-008-0754-x]
46 **Lei Y**, Li JY, Jiang J, Wang J, Zhang QY, Wang TY, Krasna MJ. Outcome of floppy Nissen fundoplication with intraoperative manometry to treat sliding hiatal hernia. *Dis Esophagus* 2008; **21**: 364-369 [PMID: 18477260 DOI: 10.1111/j.1442-2050.2007.00777.x]
47 **Cowgill SM**, Bloomston M, Al-Saadi S, Villadolid D, Rosemurgy AS. Normal lower esophageal sphincter pressure and length does not impact outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2007; **11**: 701-707 [PMID: 17436051 DOI: 10.1007/s11605-007-0152-9]
48 **Niu XP**, Yu BP, Wang YD, Han Z, Liu SF, He CY, Zhang GZ, Wu WC. Risk factors for proton pump inhibitor refractoriness in Chinese patients with non-erosive reflux disease. *World J Gastroenterol* 2013; **19**: 3124-3129 [PMID: 23716993 DOI: 10.3748/wjg.v19.i20.3124]
49 **Yang XJ**, Jiang HM, Hou XH, Song J. Anxiety and depression in patients with gastroesophageal reflux disease and their effect on quality of life. *World J Gastroenterol* 2015; **21**: 4302-4309 [PMID: 25892882 DOI: 10.3748/wjg.v21.i14.4302]
50 **Eckardt VF**. Does healing of esophagitis improve esophageal motor function? *Dig Dis Sci* 1988; **33**: 161-165 [PMID: 3338364 DOI: 10.1007/BF01535727]
51 **Savarino E**, Zentilin P, Tutuian R, Pohl D, Gemignani L, Malesci A, Savarino V. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012; **47**: 159-168 [PMID: 22038553 DOI: 10.1007/s00535-011-0480-0]
52 **Carlsson R**, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J, Haug K, de Groot G, van Oudvorst A, Dalväg A, Junghard O, Wiklund I. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. *Eur J Gastroenterol Hepatol* 1998; **10**: 119-124 [PMID: 9581986 DOI: 10.1097/00042737-199802000-00004]
53 **Galmiche JP**, Barthelemy P, Hamelin B. Treating the symptoms of gastro-oesophageal reflux disease: a double-blind comparison of omeprazole and cisapride. *Aliment Pharmacol Ther* 1997; **11**: 765-773 [PMID: 9305487 DOI: 10.1046/j.1365-2036.1997.00185.x]
54 **Desai KM**, Frisella MM, Soper NJ. Clinical outcomes after laparoscopic antireflux surgery in patients with and without preoperative endoscopic esophagitis. *J Gastrointest Surg* 2003; **7**: 44-51; discussion 51-52 [PMID: 12559184 DOI: 10.1016/S1091-255X(02)00135-X]
55 **Csendes A**. Surgical treatment of Barrett's esophagus: 1980-2003. *World J Surg* 2004; **28**: 225-231 [PMID: 14961203 DOI: 10.1007/s00268-003-6986-8]
56 **Cowgill SM**, Al-Saadi S, Villadolid D, Zervos EE, Rosemurgy AS. Does Barrett's esophagus impact outcome after laparoscopic Nissen

fundoplication? *Am J Surg* 2006; **192**: 622-626 [PMID: 17071195 DOI: 10.1016/j.amjsurg.2006.08.010]
57 **Abbas AE**, Deschamps C, Cassivi SD, Allen MS, Nichols FC, Miller DL, Pairolero PC. Barrett's esophagus: the role of laparoscopic fundoplication. *Ann Thorac Surg* 2004; **77**: 393-396 [PMID: 14759403 DOI: 10.1016/S0003-4975(03)01352-3]
58 **Oelschlager BK**, Barreca M, Chang L, Oleynikov D, Pellegrini CA. Clinical and pathologic response of Barrett's esophagus to laparoscopic antireflux surgery. *Ann Surg* 2003; **238**: 458-464; discussion 464-466 [PMID: 14530718 DOI: 10.1097/01.sla.0000090443.97693.c3]
59 **Tolone S**, Limongelli P, Romano M, Federico A, Docimo G, Ruggiero R, Brusciano L, Del Genio G, Docimo L. The patterns of reflux can affect regression of non-dysplastic and low-grade dysplastic Barrett's esophagus after medical and surgical treatment: a prospective case-control study. *Surg Endosc* 2015; **29**: 648-657 [PMID: 25030477 DOI: 10.1007/s00464-014-3713-5]
60 **Savarino E**, Gemignani L, Pohl D, Zentilin P, Dulbecco P, Assandri L, Marabotto E, Bonfanti D, Inferrera S, Fazio V, Malesci A, Tutuian R, Savarino V. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2011; **34**: 476-486 [PMID: 21671968 DOI: 10.1111/j.1365-2036.2011.04742.x]
61 **Martinucci I**, de Bortoli N, Giacchino M, Bodini G, Marabotto E, Marchi S, Savarino V, Savarino E. Esophageal motility abnormalities in gastroesophageal reflux disease. *World J Gastrointest Pharmacol Ther* 2014; **5**: 86-96 [PMID: 24868489 DOI: 10.4292/wjgpt.v5.i2.86]
62 **Heider TR**, Behrns KE, Koruda MJ, Shaheen NJ, Lucktong TA, Bradshaw B, Farrell TM. Fundoplication improves disordered esophageal motility. *J Gastrointest Surg* 2003; **7**: 159-163 [PMID: 12600439 DOI: 10.1016/S1091-255X(02)00145-2]
63 **Rydberg L**, Ruth M, Lundell L. Does oesophageal motor function improve with time after successful antireflux surgery? Results of a prospective, randomised clinical study. *Gut* 1997; **41**: 82-86 [PMID: 9274477]
64 **Chrysos E**, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A, Xynos E. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? *J Am Coll Surg* 2003; **197**: 8-15 [PMID: 12831918 DOI: 10.1016/S1072-7515(03)00151-0]
65 **Scheffer RC**, Samsom M, Frakking TG, Smout AJ, Gooszen HG. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. *Br J Surg* 2004; **91**: 1466-1472 [PMID: 15386318 DOI: 10.1002/bjs.4759]
66 **Jobe BA**, Wallace J, Hansen PD, Swanstrom LL. Evaluation of laparoscopic Toupet fundoplication as a primary repair for all patients with medically resistant gastroesophageal reflux. *Surg Endosc* 1997; **11**: 1080-1083 [PMID: 9348378 DOI: 10.1007/s004649900534]
67 **Karim SS**, Panton ON, Finley RJ, Graham AJ, Dong S, Storseth C, Clifton J. Comparison of total versus partial laparoscopic fundoplication in the management of gastroesophageal reflux disease. *Am J Surg* 1997; **173**: 375-378 [PMID: 9168069 DOI: 10.1016/S0002-9610(97)00078-0]
68 **D'Alessio MJ**, Rakita S, Bloomston M, Chambers CM, Zervos EE, Goldin SB, Poklepovic J, Boyce HW, Rosemurgy AS. Esophagography predicts favorable outcomes after laparoscopic Nissen fundoplication for patients with esophageal dysmotility. *J Am Coll Surg* 2005; **201**: 335-342 [PMID: 16125065 DOI: 10.1016/j.jamcollsurg.2005.04.036]
69 **Pizza F**, Rossetti G, Del Genio G, Maffettone V, Brusciano L, Del Genio A. Influence of esophageal motility on the outcome of laparoscopic total fundoplication. *Dis Esophagus* 2008; **21**: 78-85 [PMID: 18197944 DOI: 10.1111/j.1442-2050.2007.00756.x]
70 **Riedl O**, Gadenstätter M, Lechner W, Schwab G, Marker M, Ciovica R. Preoperative lower esophageal sphincter manometry data neither impact manifestations of GERD nor outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2009; **13**: 1189-1197 [PMID: 19370381 DOI: 10.1007/s11605-009-0890-y]
71 **Patti MG**, Perretta S, Fisichella PM, D'Avanzo A, Galvani C, Gorodner V, Way LW. Laparoscopic antireflux surgery: preoperative lower esophageal sphincter pressure does not affect outcome. *Surg Endosc* 2003; **17**: 386-389 [PMID: 12436239 DOI: 10.1007/s00464-002-8934-3]
72 **Tolone S**, De Bortoli N, Marabotto E, de Cassan C, Bodini G, Roman S, Furnari M, Savarino V, Docimo L, Savarino E. Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value? *Neurogastroenterol Motil* 2015; **27**: 1423-1431 [PMID: 26227513 DOI: 10.1111/nmo.12638]
73 **Wang D**, Patel A, Mello M, Shriver A, Gyawali CP. Esophagogastric junction contractile integral (EGJ-CI) quantifies changes in EGJ barrier function with surgical intervention. *Neurogastroenterol Motil* 2016; **28**: 639-646 [PMID: 26768087 DOI: 10.1111/nmo.12757]
74 **Fein M**, Hagen JA, Ritter MP, DeMeester TR, De Vos M, Bremner CG, Peters JH. Isolated upright gastroesophageal reflux is not a contraindication for antireflux surgery. *Surgery* 1997; **122**: 829-835 [PMID: 9347863 DOI: 10.1016/S0039-6060(97)90094-5]
75 **Saraswat VA**, Dhiman RK, Mishra A, Naik SR. Correlation of 24-hr esophageal pH patterns with clinical features and endoscopy in gastroesophageal reflux disease. *Dig Dis Sci* 1994; **39**: 199-205 [PMID: 8281858 DOI: 10.1007/BF02090083]
76 **Campos GM**, Peters JH, DeMeester TR, Oberg S, Crookes PF, Mason RJ. The pattern of esophageal acid exposure in gastroesophageal reflux disease influences the severity of the disease. *Arch Surg* 1999; **134**: 882-887; discussion 882-887 [PMID: 10443813 DOI: 10.1001/archsurg.134.8.882]
77 **DeMeester TR**, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg* 1986; **204**: 9-20 [PMID: 3729589 DOI: 10.1097/00000658-198607000-00002]
78 **Gillen P**, Thornton J, Byrne PJ, Walsh TN, Hennessy TP. Implications of upright gastro-oesophageal reflux. *Br J Surg* 1994; **81**: 239-240 [PMID: 8156346 DOI: 10.1002/bjs.1800810226]
79 **Mughal MM**, Bancewicz J, Marples M. Oesophageal manometry and pH recording does not predict the bad results of Nissen fundoplication. *Br J Surg* 1990; **77**: 43-45 [PMID: 2302512 DOI: 10.1002/bjs.1800770115]
80 **Meneghetti AT**, Tedesco P, Galvani C, Gorodner MV, Patti MG. Outcomes after laparoscopic Nissen fundoplication are not influenced by the pattern of reflux. *Dis Esophagus* 2008; **21**: 165-169 [PMID: 18269653 DOI: 10.1111/j.1442-2050.2007.00770.x]
81 **Hong D**, Swanstrom LL, Khajanchee YS, Pereira N, Hansen PD. Postoperative objective outcomes for upright, supine, and bipositional reflux disease following laparoscopic nissen fundoplication. *Arch Surg* 2004; **139**: 848-852; discussion 852-854 [PMID: 15302694 DOI: 10.1001/archsurg.139.8.848]
82 **Power C**, Maguire D, McAnena O. Factors contributing to failure of laparoscopic Nissen fundoplication and the predictive value of preoperative assessment. *Am J Surg* 2004; **187**: 457-463 [PMID: 15041491 DOI: 10.1016/j.amjsurg.2003.12.034]
83 **Cowgill SM**, Al-Saadi S, Villadolid D, Arnaoutakis D, Molloy D, Rosemurgy AS. Upright, supine, or bipositional reflux: patterns of reflux do not affect outcome after laparoscopic Nissen fundoplication. *Surg Endosc* 2007; **21**: 2193-2198 [PMID: 17522933 DOI: 10.1007/s00464-007-9333-6]
84 **Zerbib F**, Roman S, Ropert A, des Varannes SB, Pouderoux P, Chaput U, Mion F, Vérin E, Galmiche JP, Sifrim D. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol* 2006; **101**: 1956-1963 [PMID: 16848801 DOI: 10.1111/j.1572-0241.2006.00711.x]
85 **Mainie I**, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 2006; **55**: 1398-1402 [PMID: 16556669 DOI: 10.1136/gut.2005.087668]
86 **Mainie I**, Tutuian R, Agrawal A, Adams D, Castell DO. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006; **93**: 1483-1487 [PMID:

17051602 DOI: 10.1002/bjs.5493]

87 **del Genio G**, Tolone S, del Genio F, Aggarwal R, d'Alessandro A, Allaria A, Rossetti G, Brusciano L, del Genio A. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. *J Gastrointest Surg* 2008; **12**: 1491-1496 [PMID: 18612705 DOI: 10.1007/s11605-008-0583-y]

88 **Frazzoni M**, Piccoli M, Conigliaro R, Manta R, Frazzoni L, Melotti G. Refractory gastroesophageal reflux disease as diagnosed by impedance-pH monitoring can be cured by laparoscopic fundoplication. *Surg Endosc* 2013; **27**: 2940-2946 [PMID: 23436097 DOI: 10.1007/s00464-013-2861-3]

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Pitfalls in histoacryl glue injection therapy for oesophageal, gastric and ectopic varices: A review

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Abstract

Histoacryl glue is used increasingly for the treatment of gastric and ectopic varices, and there is experience in its use for oesophageal varices. It is an effective treatment, yet numerous reports of complications have accumulated. This review of the literature describes the technique, explores circulatory and vascular consideration unique to portal hypertension and categorises the complications into: "Embolisation", "local venous thrombosis", "fistulisation and extravascular injection", "ulceration, erosion and extrusion", and "nidus of infection". A case is then made for standardisation of the technique and the consent process.

Key words: Complications; Embolisation; Thrombosis; Sepsis

Core tip: N-butyl-2-cyanoacrylate (Histoacryl "glue") injection is of proven efficacy for the treatment of bleeding gastric varices but its utility in bleeding oesophageal varices remains unproven. Overall complication rates are 0.5%-5%, 1% being commonly quoted. Complications include pulmonary and systemic arterial embolisation, portal and mesenteric vein thrombosis, persistent sepsis, fistulisation and mucosal erosion due to extravascular injection, and late extrusion or variceal ulceration. Consent processes and injection techniques vary according to local experience, and there is a case for national/international agreement to standardise these.

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INTRODUCTION

Histoacryl glue therapy is licensed in the United Kindom for emergency treatment of bleeding varices. Its chemical composition is a monomer, *n*-butyl-2-

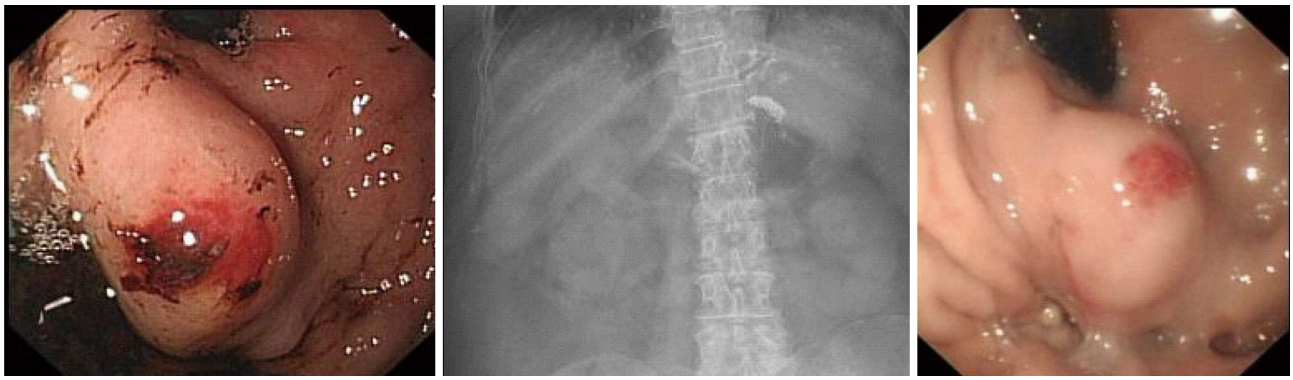

Figure 1 Endoscopic images of a gastric varix before and after glue therapy. The varix has become smaller and is now firm when probed. The plain radiograph between demonstrates a radio-opaque deposit in the fundus of the stomach, due to lipiodol.

cyanoacrylate, which polymerises into a solid mass in contact with ionic materials including water or blood. This obturates, or fills, the vascular lumen and also encourages local thrombosis. It is used first line in gastric and ectopic varices (for emergency haemostasis and secondary prophylaxis) and second line for oesophageal varices (where banding is not possible due to degraded oesophageal tissue or previous failed banding attempts). There is a solid evidence base to support the use of glue in gastric varices with numerous case series[1-8] and randomised controlled trials[9-13] indicating that efficacy of haemostasis is over 80%-90%. Data comparing gastric variceal glue injection with transjugular intrahepatic portosystemic stent shunt (TIPSS) is relatively scarce. Lo *et al*[14] performed a prospective case controlled trial in patients who had presented with acute GV bleeding and who had been stabilised with vasoconstrictors and endotherapy (not glue). They found long term superiority for TIPSS in terms of rebleeding at 33 mo (11% *vs* 38%, $P = 0.01$), but equivalent survival. A retrospective study found fewer rebleeds in the TIPSS group at 6 mo (15% *vs* 30%, $P = 0.005$), but again no differences in survival. A cost analysis showed far higher resource implications for TIPSS [$4138 United States dollars ($3009-$8290 United States dollars)] for glue *vs* $11906 United States dollars ($8200-$16770 United States dollars)[15].

The use of glue in the oesophagus is more controversial, although one series by Cipolletta *et al*[16] reported good results in 133 patients who had primary oesophageal injection of undiluted glue. Glue has also been used successfully in babies and infants less than 2 years old[17].

TECHNIQUE

Histoacryl glue is commonly mixed with lipiodol which slows the polymerisation process, allowing more time for injection, and being radio-opaque also permits post-procedural radiological examination. Precise technique varies across units both nationally and internationally. At the authors' centre 0.5 mL glue aliquots are mixed with 1 mL of lipiodol in small syringes. Saline can be injected into the variceal lumen initially to confirm an intra-luminal position at this point. Glue/lipiodol mixture is then injected 1.5 mL at a time, the number of syringes depending on the size of the varix. Further saline is injected which detaches the glue from the end of the needle and reduces the chance of tearing the glue through the variceal wall on removal of the needle. Some endoscopists prefer to inject glue as they leave the lumen, thus sealing the injection site and maintaining a view of the needle before withdrawing completely. The varix is observed, and it is not unusual to see some self-limiting bleeding through the injection site. Further injections are administered into different parts of the varix if necessary, the intention being to render the varix "solid". This is determined by probing with varix with an injection needle (needle withdrawn). The role of endoscopic ultrasound in facilitating injection when the view is obscured by blood in the stomach, or to provide a more accurate assessment of vascularity during and after injection, has been explored[18]. Real-time fluoroscopy to assess for possible embolisation has also been described, but this is better suited to elective re-injection of gastric varices and less achievable in the emergent scenario[19].

Great care should be taken by staff when preparing the glue. Any contact with the sclera or cornea can cause permanent injury, so goggles or full face masks should be used, and protocol for eye-washing well rehearsed. Patients with iodine allergies cannot receive Lipiodol. Permanent damage can also be done to the endoscope if glue polymerises in the working channel. Before the injection needle is withdrawn through the instrument the needle lumen should be flushed thoroughly. Small residues of polymerised glue may be visible on the tip of the needle, but this does not usually cause a problem.

The ideal outcome after treatment of gastric varices is illustrated in Figure 1. An 85-year-old lady who presented with haematemesis and encephalopathy was found to have a fundal gastric varix with a red sign. It was injected with 3 mL × 1.5 mL aliquots of glue/lipiodol. A plain X-ray demonstrated a well circumscribed "clot" of glue in the fundus, with additional strands in

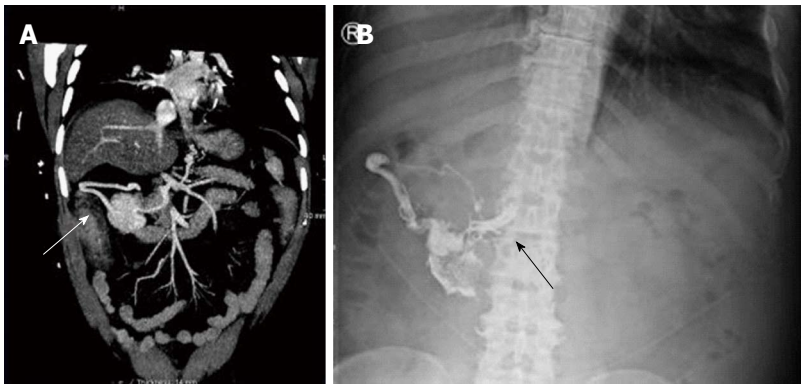

Figure 2 Duodenal varix on computed tomography and plain radiograph before and after glue injection. A: Computed tomography angiogram showing a large abdominal varix meeting the duodenum (white arrow); B: After glue injection a plain radiograph showed lipiodol/glue in the same vessel, with extension medially up to the portal vein (black arrow).

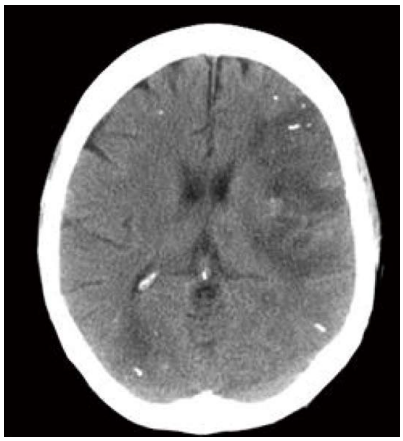

Figure 3 Computed tomogram of brain following glue/lipiodol injection. There are high signal deposits peripherally following embolisation of glue.

oesophageal vessels above. At check endoscopy 7 d later the varix was smaller and appeared "safe".

VASCULAR CONSIDERATIONS

The propensity for glue in its liquid phase to spread along vessels distal and proximal to the bleeding varix should be emphasised, as this is relevant to the phenomena of local venous thrombosis and distant embolization. Specific haemodynamic features of cirrhotic patients such as hyperdynamic circulation, presence of porto-systemic shunts and dilated pulmonary vessels may also be implicated in these events.

Figure 2 illustrates how glue can spread into feeding and draining vessels. A computed tomography (CT) angiogram (Figure 2A) performed on a cirrhotic patient who had a negative index endoscopy shows a large varix indenting the wall of the second part of duodenum, but without active extravasation. Figure 2B is a plain X-ray taken following injection of 9 mL histacryl glue into a large, actively bleeding duodenal varix that was identified at second endoscopy several hours later. A plain abdominal X-ray delineated the extent of lipiodol/histoacryl, which filled the varix and extended towards the portal vein, probably representing a dilated pancreato-duodenal vein. This patient recovered and experienced no adverse effects.

In this review we categorise reported complications based on published reports, and will include illustrative examples of cases that the authors have been involved with.

COMPLICATIONS

Overview and incidence

Cheng *et al*[20], in a study focussed on complications, documented 51 adverse events in 753 treated patients (6.7%), 33 of these being early re-bleeds related to extrusion of glue within 3 mo. Overall complication related mortality was 0.53%. A study examining factors influencing outcomes (n = 90) found early complications in 14.4%, mostly infective and not clearly related to injection - however systemic embolisation occurred in 4.4%[5]. The American Society for Gastrointestinal Endoscopy, in its technical evaluation report of 2013[21], did not support the use of glue for oesophageal varices due to sporadic reports of complications. Embolisation is the most frequently mentioned complication during the consent process (author's experience), a 1% risk being commonly quoted based on reviews which are explored below, but there is little certainty regarding other types of complications. Although most studies emphasise that the technique is safe, numerous reports describe unexpected early and delayed complications some of which are fatal.

Embolisation

A retrospective review looking at 25-year experience with glue injection by Saraswat *et al*[2] identified a risk of embolisation in the range 0.5%-4.3%. Cheng *et al*[20]'s large review of 753 cases identified distant embolisation in 5 patients (0.7%; 1 pulmonary, 1 brain, and 3 splenic). Fatal sepsis related to splenic infarction was reported in an isolated report[22].

Embolisation to the right atrium or pulmonary arteries has been reported by several authors[23-25], including one fatal case[26]. Chew *et al*[27] describe a patient who developed sudden hypoxia 10 d after injection. In this case solid particles must have become detached from the primary mass of glue. In contrast, the patient in whose care one of the authors was involved became hypoxic during the injection procedure and suffered runs of ventricular tachycardia which self-

Figure 4 Endoscopic appearances of oesophagus following glue injection for refractory variceal haemorrhage. There is ulceration and early cavitation in the first image which progresses and is severe 5 d later.

terminated. A post-procedural X-ray demonstrated glue in the pulmonary vasculature[23].

Cerebral embolisation has been reported several times. Upadhyay *et al*[28] described a patient who developed cortical blindness (as well as acute myocardial infarction), attributed to glue emboli. Sée *et al*[29] reported two cases of cerebral embolization (one fatal), and Roesch *et al*[30] reported simultaneous pulmonary, cerebral and coronary events. An intubated and ventilated patient one of the authors treated did not wake up appropriately following injection of a gastric varix. A CT scan of the brain revealed multiple peripheral radio-opaque deposits (Figure 3). An echocardiogram revealed an atrial septal defect, the likely explanation for cross over from the portal to the systemic arterial circulation, *via* the systemic venous return. The patient succumbed to multi-organ failure secondary to decompensated liver disease. In the absence of septal defects it is not easy to explain how glue moves into the systemic arterial circulation, but Sée *et al*[29] hypothesised that glue may travel *via* dilated pulmonary vessels which are known to develop in cirrhosis (associated with hepatopulmonary syndrome).

Local venous thrombosis

Belletrutti *et al*[6] in their large review of patients in North America treated for gastric varices reported one case of superior mesenteric vein thrombosis. Mosca *et al*[7] reported one case of acute splenic vein thrombosis in their series of 65 patients treated for gastric varices. Liu *et al*[31] also reported splenic vein thrombosis in association with Klebsiella septicaemia. Shih *et al*[32] presented a case of portal vein thrombosis and progressive liver atrophy after cyanoacrylate injection. Shim *et al*[33] noted combined portal and splenic vein thrombosis in their report. Thrombosis of portomesenteric vessels is not surprising, given their proximity and intimate relation to porto-systemic collaterals that form oesophagogastric varices. Case reports have not described morbidity or mortality due to organ ischaemia secondary to vascular impingement, although experience would suggest new PVT can only be disadvantageous to cirrhosis patients.

Fistulisation and extravascular injection

Late fistulisation to a pulmonary vein following oesophageal injection was reported by Barclay *et al*[34]. This must have occurred following extra-vascular injection into the mediastinum. Retrogastric abscess formation following gastric variceal injection has been reported[35]. One of the authors has seen glue in the pleural space and in the para-oesophageal tissues (unpublished). In neither of these cases were there any short or medium term adverse consequences. The use of glue in refractory oesophageal variceal bleeding is more difficult and prone to inadvertent injection through the oesophageal wall into adjacent structures. Whereas gastric varices present an easily definable vessel, and the presence of the injection needle within the lumen can be confirmed with saline injections, oesophageal varices have usually been banded already and there may be considerable ulceration and mucosal trauma. Injections may be semi-blind or intended to enter intramural feeding vessels. Glue has also been used to "seal" the edges of post-banding ulcers that are found to be oozing. A report by Kim *et al*[36] described sinus formation after treatment for this indication.

Ulceration, erosion and extrusion

Choudhuri *et al*[3] identified ulceration of gastric varices in 32 of 170 injected patients, but did not attribute specific morbidity to this. Sharma *et al*[37] reported late bleeding from a glue ulcer. The authors' experience suggests that ulceration is more troublesome after glue injection into the oesophagus, where extra-luminal injection is far more likely due to the difficultly in delineating the variceal columns. In one case, serial endoscopies identified increasing cavitation around a nidus of solid glue (Figure 4). This patient suffered ongoing decompensation and intermittent bleeding, dying from multiple organ failure two weeks after the initial treatment of bleeding. He was chronically encephalopathic and could not undergo TIPSS.

A large series (n = 168) reported by Wang *et al*[38] found early re-bleeding associated with "rejection" of glue in 9 (6.2%) at less than two months, and extrusion in a further 12 (8.1% at 2-18 mo). This study appeared to suggest that extrusion of glue casts into the gastric lumen is common, almost inevitable. There were cases of late re-bleeding, although persistent obturation of the variceal lumen was confirmed in the majority. The study of over 700 patients by Cheng *et al*[20] documented re-

bleeding associated with "early extrusion" (*i.e.*, less than 3 mo) in 33 (4.4%). One of these patients died.

Laceration of varix due to banding of an unrecognised glue deposit

One case report[39] has described inadvertent laceration of an oesophageal varix during band ligation, due to the presence of glue from a previous treatment session. This highlights the fact that glue is permanent, and it should be noted prior to future interventions.

Stricture

A single case of oesophageal impaction[40] following glue injection into a gastric varix was described over ten years ago.

Nidus of sepsis

There are several reports of chronic sepsis associated with glue, and a particular case reported by Wright *et al*[41] resulted in recurrent sepsis episodes with extended spectrum β-lactamase-producing *Escherichia* following injection of a gastric varix. Imaging showed glue deposits in the fundal varix itself, the IVC and the left renal vein. The patient required 6 wk of parenteral antibiotic therapy before the sepsis was cleared. The case of splenic vein thrombosis reported by Liu *et al*[31] was associated with *Klebsiella* septicaemia. Hamad *et al*[42] described sepsis in association the embolic events, while Chang *et al*[43] identified portal vein thrombosis following injection as a source of continued sepsis.

CONCLUSION

The attractions of glue therapy include an evidence base for its efficacy, the ability to learn the technique by adapting common endoscopic skills, and the option to offer haemostatic therapy to patients who would otherwise require emergency transfer to a tertiary unit for consideration of TIPSS. Sadly, many patients are not candidates for TIPSS due to co-morbidity or the severity of liver failure, which leaves glue injection as the only remaining therapeutic option. Training in glue injection therapy is ad hoc, relying on the presence of trainees when patients present as emergencies. Planned glue sessions do occur, during following after treatment of large gastric varices, but the numbers are small.

Seewald *et al*[44] proposed several standardised steps, including dilution ratios, aliquot volumes and injection number. Agreed standards which include indications, recommended consent details and technical approach would ensure that trainees experience some consistency, would enlarge the foundation of experience on which informed consent is based and protect practitioners in the event of adverse outcomes.

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REFERENCES

1 **Lo GH**, Lin CW, Perng DS, Chang CY, Lee CT, Hsu CY, Wang HM, Lin HC. A retrospective comparative study of histoacryl injection and banding ligation in the treatment of acute type 1 gastric variceal hemorrhage. *Scand J Gastroenterol* 2013; **48**: 1198-1204 [PMID: 24047398 DOI: 10.3109/00365521.2013.832792]

2 **Saraswat VA**, Verma A. Gluing gastric varices in 2012: lessons learnt over 25 years. *J Clin Exp Hepatol* 2012; **2**: 55-69 [PMID: 25755406 DOI: 10.1016/S0973-6883(12)60088-7]

3 **Choudhuri G**, Chetri K, Bhat G, Alexander G, Das K, Ghoshal UC, Das K, Chandra P. Long-term efficacy and safety of N-butylcyanoacrylate in endoscopic treatment of gastric varices. *Trop Gastroenterol* 2010; **31**: 155-164 [PMID: 21560518]

4 **Al-Ali J**, Pawlowska M, Coss A, Svarta S, Byrne M, Enns R. Endoscopic management of gastric variceal bleeding with cyanoacrylate glue injection: safety and efficacy in a Canadian population. *Can J Gastroenterol* 2010; **24**: 593-596 [PMID: 21037987 DOI: 10.1155/2010/276273]

5 **Prachayakul V**, Aswakul P, Chantarojanasiri T, Leelakusolvong S. Factors influencing clinical outcomes of Histoacryl® glue injection-treated gastric variceal hemorrhage. *World J Gastroenterol* 2013; **19**: 2379-2387 [PMID: 23613633 DOI: 10.3748/wjg.v19.i15.2379]

6 **Belletrutti PJ**, Romagnuolo J, Hilsden RJ, Chen F, Kaplan B, Love J, Beck PL. Endoscopic management of gastric varices: efficacy and outcomes of gluing with N-butyl-2-cyanoacrylate in a North American patient population. *Can J Gastroenterol* 2008; **22**: 931-936 [PMID: 19018339 DOI: 10.1155/2008/389517]

7 **Mosca I**, Ligorría R, Tufare F, Villaverde A, Baldoni F, Martínez H, Chopita N. N-butyl-2-cyanoacrylate for the treatment of gastric varices. *Acta Gastroenterol Latinoam* 2012; **42**: 27-32 [PMID: 22616494]

8 **Procaccini NJ**, Al-Osaimi AM, Northup P, Argo C, Caldwell SH. Endoscopic cyanoacrylate versus transjugular intrahepatic portosystemic shunt for gastric variceal bleeding: a single-center U.S. analysis. *Gastrointest Endosc* 2009; **70**: 881-887 [PMID: 19559425 DOI: 10.1016/j.gie.2009.03.1169]

9 **Sarin SK**, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002; **97**: 1010-1015 [PMID: 12003381 DOI: 10.1016/s0002-9270(02)03978-3]

10 **Lo GH**, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001; **33**: 1060-1064 [PMID: 11343232 DOI: 10.1053/jhep.2001.24116]

11 **Tan PC**, Hou MC, Lin HC, Liu TT, Lee FY, Chang FY, Lee SD. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatology* 2006; **43**: 690-697 [PMID: 16557539 DOI: 10.1002/hep.21145]

12 **Mishra SR**, Chander Sharma B, Kumar A, Sarin SK. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial. *Gut* 2010; **59**: 729-735 [PMID: 20551457 DOI: 10.1136/gut.2009.192039]

13 **Mishra SR**, Sharma BC, Kumar A, Sarin SK. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. *J Hepatol* 2011; **54**: 1161-1167 [PMID: 21145834 DOI: 10.1016/j.jhep.2010.09.031]

14 **Lo GH**, Liang HL, Chen WC, Chen MH, Lai KH, Hsu PI, Lin CK, Chan HH, Pan HB. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. *Endoscopy*

2007; **39**: 679-685 [PMID: 17661241 DOI: 10.1055/s-2007-966591]
15 **Mahadeva S**, Bellamy MC, Kessel D, Davies MH, Millson CE. Cost-effectiveness of N-butyl-2-cyanoacrylate (histoacryl) glue injections versus transjugular intrahepatic portosystemic shunt in the management of acute gastric variceal bleeding. *Am J Gastroenterol* 2003; **98**: 2688-2693 [PMID: 14687818 DOI: 10.1111/j.1572-0241.2003.08769.x]
16 **Cipolletta L**, Zambelli A, Bianco MA, De Grazia F, Meucci C, Lupinacci G, Salerno R, Piscopo R, Marmo R, Orsini L, Rotondano G. Acrylate glue injection for acutely bleeding oesophageal varices: A prospective cohort study. *Dig Liver Dis* 2009; **41**: 729-734 [PMID: 19362522 DOI: 10.1016/j.dld.2009.02.006]
17 **Rivet C**, Robles-Medranda C, Dumortier J, Le Gall C, Ponchon T, Lachaux A. Endoscopic treatment of gastroesophageal varices in young infants with cyanoacrylate glue: a pilot study. *Gastrointest Endosc* 2009; **69**: 1034-1038 [PMID: 19152910 DOI: 10.1016/j.gie.2008.07.025]
18 **Bhatia V**. Endoscopic Ultrasound (EUS) for Esophageal and Gastric Varices: How Can it Improve the Outcomes and Reduce Complications of Glue Injection. *J Clin Exp Hepatol* 2012; **2**: 70-74 [PMID: 25755407 DOI: 10.1016/s0973-6883(12)60083-8]
19 **Gubler C**, Bauerfeind P. Safe and successful endoscopic initial treatment and long-term eradication of gastric varices by endoscopic ultrasound-guided Histoacryl (N-butyl-2-cyanoacrylate) injection. *Scand J Gastroenterol* 2014; **49**: 1136-1142 [PMID: 24947448 DOI: 10.3109/00365521.2014.929171]
20 **Cheng LF**, Wang ZQ, Li CZ, Lin W, Yeo AE, Jin B. Low incidence of complications from endoscopic gastric variceal obturation with butyl cyanoacrylate. *Clin Gastroenterol Hepatol* 2010; **8**: 760-766 [PMID: 20621678 DOI: 10.1016/j.cgh.2010.05.019]
21 **Bhat YM**, Banerjee S, Barth BA, Chauhan SS, Gottlieb KT, Konda V, Maple JT, Murad FM, Pfau PR, Pleskow DK, Siddiqui UD, Tokar JL, Wang A, Rodriguez SA. Tissue adhesives: cyanoacrylate glue and fibrin sealant. *Gastrointest Endosc* 2013; **78**: 209-215 [PMID: 23867370 DOI: 10.1016/j.gie.2013.04.166]
22 **Martins Santos MM**, Correia LP, Rodrigues RA, Lenz Tolentino LH, Ferrari AP, Della Libera E. Splenic artery embolization and infarction after cyanoacrylate injection for esophageal varices. *Gastrointest Endosc* 2007; **65**: 1088-1090 [PMID: 17451707 DOI: 10.1016/j.gie.2006.10.008]
23 **Berry PA**, Cross TJ, Orr DW. Clinical challenges and images in GI. Pulmonary embolization of histoacryl "glue" causing hypoxia and cardiovascular instability. *Gastroenterology* 2007; **133**: 1413, 1748 [PMID: 17983799 DOI: 10.1053/j.gastro.2007.09.051]
24 **Miyakoda K**, Takedatsu H, Emori K, Inoue H, Toyonaga A, Mitsuyama K, Tsuruta O, Sata M. N-butyl-2-cyanoacrylate (histoacryl) glue in the right atrium after endoscopic injection for a ruptured duodenal varix: complication of histoacryl injection. *Dig Endosc* 2012; **24**: 192 [PMID: 22507099 DOI: 10.1111/j.1443-1661.2011.01185.x]
25 **Javed A**, Salamat A. N-butyl-2-cyanoacrylate and lipoidol pulmonary embolism (glue embolism). *J Ayub Med Coll Abbottabad* 2008; **20**: 143-145 [PMID: 19385481]
26 **Ashraf P**, Haqqi SA, Shaikh H, Wakani AJ. Glue embolism: a rare cause of pulmonary embolism. *J Coll Physicians Surg Pak* 2011; **21**: 574-576 [PMID: 21914421]
27 **Chew JR**, Balan A, Griffiths W, Herre J. Delayed onset pulmonary glue emboli in a ventilated patient: a rare complication following endoscopic cyanoacrylate injection for gastric variceal haemorrhage. *BMJ Case Rep* 2014; **2014:** pii: bcr2014206461 [PMID: 25320260 DOI: 10.1136/bcr-2014-206461]
28 **Upadhyay AP**, Ananthasivan R, Radhakrishnan S, Zubaidi G. Cortical blindness and acute myocardial infarction following injection of bleeding gastric varices with cyanoacrylate glue. *Endoscopy* 2005; **37**: 1034 [PMID: 16189782 DOI: 10.1055/s-2005-870211]
29 **Sée A**, Florent C, Lamy P, Lévy VG, Bouvry M. Cerebrovascular accidents after endoscopic obturation of esophageal varices with isobutyl-2-cyanoacrylate in 2 patients. *Gastroenterol Clin Biol* 1986; **10**: 604-607 [PMID: 3781162]
30 **Roesch W**, Rexroth G. Pulmonary, cerebral and coronary emboli during bucrylate injection of bleeding fundic varices. *Endoscopy* 1998; **30**: S89-S90 [PMID: 9865574 DOI: 10.1055/s-2007-1001406]
31 **Liu CH**, Tsai FC, Liang PC, Lee CZ, Yang PM. Splenic vein thrombosis and Klebsiella pneumoniae septicemia after endoscopic gastric variceal obturation therapy with N-butyl-2-cyanoacrylate. *Gastrointest Endosc* 2006; **63**: 336-338 [PMID: 16427952 DOI: 10.1016/j.gie.2005.08.025]
32 **Shih KL**, Yen HH, Soon MS. Portal-vein embolization after sclerotherapy treatment of bleeding gastric varices: report of a case with long-term follow-up. *Gastrointest Endosc* 2009; **69**: 1176-1178 [PMID: 19152907 DOI: 10.1016/j.gie.2008.07.006]
33 **Shim CS**, Cho YD, Kim JO, Bong HK, Kim YS, Lee JS, Lee MS, Hwang SG. A case of portal and splenic vein thrombosis after Histoacryl injection therapy in gastric varices. *Endoscopy* 1996; **28**: 461 [PMID: 8858240 DOI: 10.1055/s-2007-1005514]
34 **Barclay S**, Cameron I, Stewart I, Forrest E. Massive hemorrhage from a pulmonary vein-esophageal fistula: a late complication of Histoacryl glue injection. *Gastrointest Endosc* 2009; **70**: 1037-1038 [PMID: 19559424 DOI: 10.1016/j.gie.2009.03.014]
35 **Verger P**, Blais J, Gruau M, Haffaf Y. Retrogastric abscess secondary to gastric varices obturation with cyanoacrylate. *Gastroenterol Clin Biol* 1998; **22**: 248-249 [PMID: 9762202]
36 **Kim EK**, Sohn JH, Kim TY, Kim BK, Yu YH, Eun CS, Jeon YC, Han DS. Esophageal sinus formation due to cyanoacrylate injection for esophageal variceal ligation-induced ulcer bleeding in a cirrhotic patient. *Korean J Gastroenterol* 2011; **57**: 180-183 [PMID: 21519166 DOI: 10.4166/kjg.2011.57.3.180]
37 **Sharma M**, Goyal A. Bleeding after glue injection in gastric varices. Rebleeding from a glue ulcer. *Gastroenterology* 2012; **142**: e1-e2 [PMID: 22549007 DOI: 10.1053/j.gastro.2011.11.043]
38 **Wang YM**, Cheng LF, Li N, Wu K, Zhai JS, Wang YW. Study of glue extrusion after endoscopic N-butyl-2-cyanoacrylate injection on gastric variceal bleeding. *World J Gastroenterol* 2009; **15**: 4945-4951 [PMID: 19842227 DOI: 10.3748/wjg.15.4945]
39 **Wei XQ**, Gu HY, Wu ZE, Miao HB, Wang PQ, Wen ZF, Wu B. Endoscopic variceal ligation caused massive bleeding due to laceration of an esophageal varicose vein with tissue glue emboli. *World J Gastroenterol* 2014; **20**: 15937-15940 [PMID: 25400482 DOI: 10.3748/wjg.v20.i42.15937]
40 **Liu TT**, Hou MC, Lin HC, Chang FY, Lee SD. Esophageal impaction: a rare complication of tissue glue injection for gastric variceal bleeding. *Endoscopy* 2001; **33**: 905 [PMID: 11571692 DOI: 10.1055/s-2001-17334]
41 **Wright G**, Matull WR, Zambreanu L, O'Neill S, Smith R, O'Beirne J, Morgan MY. Recurrent bacteremia due to retained embolized glue following variceal obliteration. *Endoscopy* 2009; **41** Suppl 2: E56-E57 [PMID: 19319779 DOI: 10.1055/s-2008-1077564]
42 **Hamad N**, Stephens J, Maskell GF, Hussaini SH, Dalton HR. Case report: Thromboembolic and septic complications of migrated cyanoacrylate injected for bleeding gastric varices. *Br J Radiol* 2008; **81**: e263-e265 [PMID: 18941038 DOI: 10.1259/bjr/30231294]
43 **Chang CJ**, Shiau YT, Chen TL, Hou MC, Sun CH, Liao WC, Lin HC, Lee SD. Pyogenic portal vein thrombosis as a reservoir of persistent septicemia after cyanoacrylate injection for bleeding gastric varices. *Digestion* 2008; **78**: 139-143 [PMID: 19023208 DOI: 10.1159/000175360]
44 **Seewald S**, Ang TL, Imazu H, Naga M, Omar S, Groth S, Seitz U, Zhong Y, Thonke F, Soehendra N. A standardized injection technique and regimen ensures success and safety of N-butyl-2-cyanoacrylate injection for the treatment of gastric fundal varices (with videos). *Gastrointest Endosc* 2008; **68**: 447-454 [PMID: 18760173 DOI: 10.1016/j.gie.2008.02.050]

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MINIREVIEWS

Impact of laparoscopic surgery training laboratory on surgeon's performance

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Abstract

Minimally invasive surgery has been replacing the open standard technique in several procedures. Similar or even better postoperative outcomes have been described in laparoscopic or robot-assisted procedures when compared to open surgery. Moreover, minimally invasive surgery has been providing less postoperative pain, shorter hospitalization, and thus a faster return to daily activities. However, the learning curve required to obtain laparoscopic expertise has been a barrier in laparoscopic spreading. Laparoscopic surgery training laboratory has been developed to aid surgeons to overcome the challenging learning curve. It may include tutorials, inanimate model skills training (box models and virtual reality simulators), animal laboratory, and operating room observation. Several different laparoscopic courses are available with specific characteristics and goals. Herein, we aim to describe the activities performed in a dry and animal-model training laboratory and to evaluate the impact of different kinds of laparoscopic surgery training courses on surgeon's performance. Several tasks are performed in dry and animal laboratory to reproduce a real surgery. A short period of training can improve laparoscopic surgical skills, although most of times it is not enough to confer laparoscopic expertise for participants. Nevertheless, this short period of training is able to increase the laparoscopic practice of surgeons in their communities. Full laparoscopic training in medical residence or fellowship programs is the best way of stimulating laparoscopic dissemination.

Key words: Education; Laboratories; Laparoscopy; Robotics; Surgery

Core tip: Laparoscopic surgery has been replacing the open standard technique in several procedures. However, the learning curve required to obtain laparoscopic expertise has been an issue in medical community. Laparoscopic surgery training laboratory was developed to overcome this barrier. Although a short period of training can improve laparoscopic surgical skills, full laparoscopic training in medical

residence or fellowship programs is the best way of stimulating laparoscopic dissemination.

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INTRODUCTION

Laparoscopic surgery has gained popularity in the last few decades, replacing open standard technique in several procedures from general surgery, gastrointestinal surgery, gynecology and urology. In fact, it has been considered standard of care in many cases such as cholecystectomy, appendectomy, colectomy, hysterectomy, pyeloplasty, nephrectomy, and others[1-5]. Laparoscopic approach has been associated with decreased postoperative pain, shorter hospitalization, faster recovery, and better cosmetics[1-5]. Although surgeons are interested in adopting laparoscopic techniques in their practices, most are lacking formal training in laparoscopy. Barriers such as new technology, inadequate training availability, concerns about complications, and willingness to negotiate learning curves make the transition to minimally invasive procedures challenging.

Currently, more realistic training opportunities involving weekend courses, video libraries, hands-on conferences, and traveling proctors are helping in laparoscopy dissemination. In addition, new generation of surgeons has been trained in laparoscopy during medical residence or fellowship programs. Inanimate models, virtual-reality simulators, and animal and cadaver laboratory have been incorporated to surgical education and are providing a positive impact on minimally invasive surgeon's performance.

Herein, we aim to describe the activities performed in a dry and animal-model training laboratory and to evaluate the impact of different kinds of laparoscopic surgery training courses on surgeon's performance.

DRY LABORATORY

Dry laboratory training comprises box models (consisting of physical inanimate materials) and virtual reality simulators (Figure 1). Similarly, there are physical and virtual reality training models available for robot-assisted laparoscopic surgery. As the fundamentals of laparoscopic surgery (*e.g.,* camera navigation, cutting, suturing, grasping) require different skills from surgeons familiarized with conventional surgery, training models begin with basic principles and can offer more sophisticated exercises, including physical or virtual simulation of complete procedures and surgeries (Figure 2). Each model has particularities regarding cost, availability and performance measures.

Evaluation of a model's validity for training includes face, content and construct validity[6]. Face validity refers to the subjective perception of a test being able to measure what it is set out to measure, which means, in the case of training models, the impression of realism. Content validity is the extent to which a test measures and represents all relevant aspects of a given construct (*i.e.*, whether a model can thoroughly evaluate all aspects of surgical skills). Construct validity refers to the ability of a test to effectively measure what it claims to measure. A manifestation of construct validity in surgical simulators is the ability of the system to differentiate novices from experts. Evaluation of a trainee performing tasks may take into account time for completion, accuracy of movements, number of movements, and distance needed to complete a given task[7,8]. Camera skills evaluation also takes into account percentage of time with optimal framing. For complex procedures, ability to finish a surgical step and complications within steps are also considered. A composite score is usually generated to evaluate the whole of the performance.

Box model training

Surgical box models consist of real instruments used for laparoscopy inserted into a box with a camera to simulate the human abdomen. The surgeon will manipulate targets inside the box that simulate tissues (*e.g.,* silicon models to mimic bowels or a bladder). Advantages of these models include low cost and high availability; trainees may even purchase models and practice at home. Another strength is the use of real instruments. Face validity is a shortcoming of this method, since rubber or silicon models used are limited in realism regarding aspects such as consistency and ability to simulate bleeding. Another drawback of the method is the limited repertoire of surgeries and the complexity of tasks that a single model can provide. Yet, to date, these models appear to be effective in improving basic technical skills in subjects with no previous experience in laparoscopic surgery. Studies with medical students have shown improvement in quality and speed of sutures[9] as well as improved camera skills after training in box models[10]. Similarly, studies have shown greater accuracy, precision and speed for cutting among novice students trained with box models[11]. Subjects appear to develop greater speed, travel lesser distances and perform lesser movements to complete tasks after training, although these results have not been replicated in all studies[12,13]. Trainees also seem to present lower error rates after training, although it is unclear whether box models or virtual reality simulators offer better results[9,12,14]. Overall, despite existence of conflicting results and the difficulty in accurately assessing improvement, box model training seems to improve performance of basic skills in laparoscopy for trainees with no previous

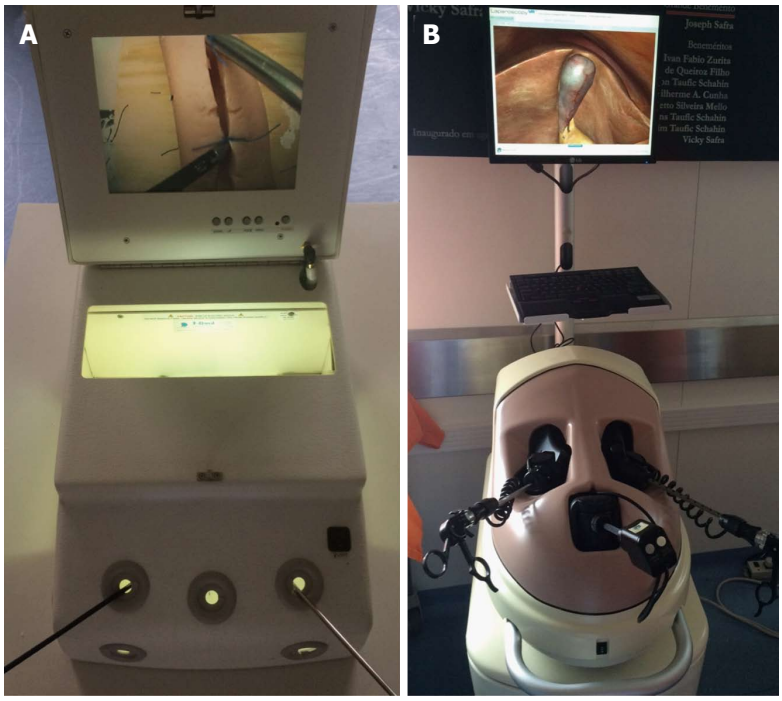

Figure 1 Laboratory tools for surgical training. A: Box training; B: Virtual reality simulator.

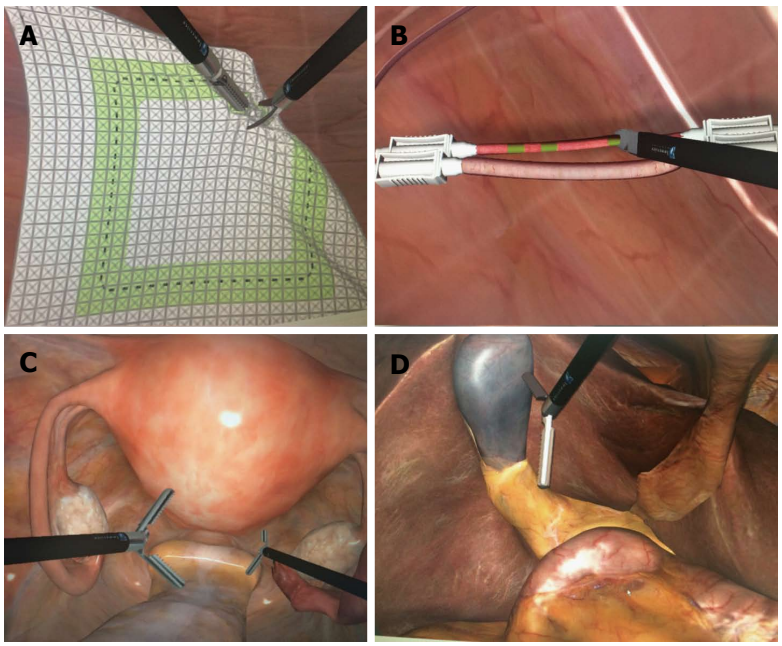

Figure 2 Virtual reality simulator. A: Cutting task; B: Clipping task; C: Hysterectomy; D: Cholecystectomy.

experience[15].

Virtual reality simulators

Virtual reality simulators (VRS) of numerous manufacturers have been released in the market. These models consist of sophisticated softwares that generate representations of laparoscopic exercises, from simple tasks to whole surgeries (*e.g.,* nephrectomy, colectomy). The trainee manipulates instruments that mimic those used in real laparoscopy. VRS have been tested and validated for face, content and construct validity[16,17]. Strengths of VRS include greater realism and the possibility of a wide range of procedures of different complexity[18]. Furthermore, performance of an individual can be recorded, measured against objective standards and compared to other trainees. However, low availability and high prices, beginning at EUR 60000 are a limitation for the widespread use of these instruments[19]. Studies have suggested that VRS provide comparable skill acquisition in relation to

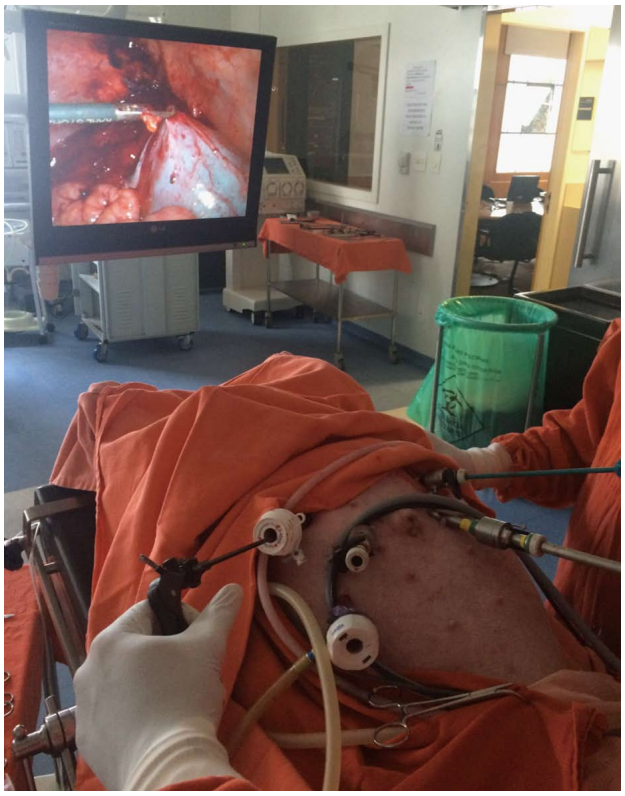

Figure 3 Pig model for laparoscopic training.

box model training, and it has also been suggested that these 2 methods may have complementary roles in laparoscopic training[11,20]. The individual role of VRS alone in final surgical performance is still unclear[21].

Robotic surgery simulators

Similar to virtual simulators of conventional laparoscopy, robotic surgery simulators have been developed and validated, offering representation of surgical tasks and incorporating the technical differences between the two surgical techniques[6,22,23]. These models share the same strengths of conventional laparoscopy VRS, especially realism and standardized evaluation. Similarly, robotic surgery simulators are of limited dispersion due to their high prices. To date, skill transfer properties of these models are still unclear[24].

ANIMAL AND CADAVER MODEL LABORATORY

Teaching minimally invasive techniques in the operating room has become increasingly difficult due to economic and patient safety concerns. Laparoscopic surgical training includes live animal training (Figure 3), animal cadaver training, training using the box-trainer and virtual reality training. Virtual reality training has been used primarily to develop component skills, *i.e.*, diathermy, clipping, suturing. It usually does not allow the student to perform the entire procedure and does not take into consideration possible anatomic variations that might be encountered. In addition, real laparoscopic instruments are not used, current technology has limitations, and high costs limit widespread applicability of virtual reality simulators. Yet, the combination of virtual and box-trainer with the animal model training might shorten the learning curve. La Torre *et al*[25] showed that the ability and time to knot-tying might be reduced if the surgeon underwent training in the virtual simulator prior to the animal model. More important, if the surgeon is exposed to repetitive animal model training, surgical time and intraoperative complications are reduced and the level of confidence and expertise measured by the global operative assessment of laparoscopic skills (GOALS) are significantly improved. Animal model training and surgeon evaluation through GOALS might be used to identify all areas of skill deficiency that require improvement. Supplementary training and mentoring can be offered to address skill deficiencies. In addition, surgeons' performances might be evaluated and compared in relation to the mean of the performances of other surgeons with the same training or those with high proficiency.

Residents usually prefer animal models for training rather than a virtual simulator model because the first are more realistic to the real scenario of operating on a patient. Tissue handling and haptic feedback are advantages compared to virtual simulators and box models. Also, intraoperative complications such as bleeding and organ lesions are only realistic in the animal model[26,27]. Zimmerman *et al*[28] evaluated 36 surgical residents of a multimodality intensive laparoscopic training course who underwent a 5-d intensive training on the porcine model and found that the post-course performance scores improved by 100% to 200% with respect to the pre-course scores. The main areas with significant interest on laparoscopic training during residency are general surgery, urology, gastrointestinal surgery, and gynecology. Since Rassweiler *et al*[29] highlighted the importance of preclinical training on pelvic trainer and animal studies before advancing to real-time laparoscopic nephrectomy, there has been an increase in number of training models being utilized and reported in literature in regards to urological procedures. The most common models for training are the porcine or chicken models[30]. Initially, authors studied the learning curve for ablative procedures such as total nephrectomy. Later, with the advancement in minimally invasive surgeries, the learning of complex surgical skills with multiple models were developed for partial nephrectomy, pyeloplasty, single port surgery, natural orifice transluminal endoscopic surgery, orthotopic renal transplants, and finally radical prostatectomy. More recently, 2-dimensional (2D) was compared to 3-dimensional (3D) laparoscopy during residence laboratory training[31]. The authors found that the 3D technology facilitated the surgical performance of inexperienced surgeons during complex laparoscopic kidney procedures on a porcine model.

Although most general surgery program directors consider skills labs effective for improving operating room performance, only half of those programs have in fact an implemented skill lab training program in the residency curriculum[32]. Torricelli *et al*[18] have demonstrated that with a 10-wk dedicated laparoscopic training program, first-year urology residents were able to perform more than one hundred procedures with low and high complexity in the porcine model under supervision of a more experienced proctor[18]. The improvements on laparoscopic skills lead to a high degree of familiarization with the actual operative field. Also, it shortens operative time, decreases operative complications and ultimately increases patient safety. In the same study, the authors emphasize that residents from more than one surgical specialty might train in the same laboratory. However, a cross-specialty training program is also feasible and has proved validity[33-35]. Benefits of this arrangement for a training program comprise more frequent disposal of courses and a more effective use of training resources.

IMPACT OF LAPAROSCOPIC TRAINING COURSES

Several different laparoscopic courses are available for surgeons who aim to improve their skills in minimally invasive surgery. There are short length courses that range from 2 to 5 d well as full year fellowship programs, which are designated for senior residents interested in laparoscopic and robotic procedures. Each course has its particularities and has proved to be able of achieving specific goals.

Asano *et al*[36] in a 2-d laparoscopic intestinal workshop including interactive discussions during live laparoscopic resection, didactic teaching, video clips and supervised hands-on practice of laparoscopic colon resection on cadaveric models reported 62.5% of participants who were not performing laparoscopic colectomies prior to the course had performed at least one 6 mo after the training. Okrainee *et al*[37] in a 3-d course described the impact of the "fundaments of laparoscopic surgery" (FLS) program in small group of 20 surgeons and trainees (general surgery, urology, and gynecology). FLS is an educational program developed by the Society of American Gastrointestinal and Endoscopic Surgeons for teaching the basic cognitive knowledge and technical skills required for laparoscopic surgery[37]. It includes a didactic component presented in a standardized fashion CD-ROM, a simulation-based technical skills component (peg transfer, pattern cutting, ligating loop, extracorporeal suture, and intracorporeal suture), and an assessment component that measures both cognitive and technical skills. In this course, although the mean posttest scores were significantly higher than pretests for each FLS task and for the total normalized FLS simulator score, only two surgeons achieved a passing score on both cognitive and skills assessment required to obtain FLS certification. This study indicates that FLS course can positively impact on surgeons' performance, however a longer period of training is probably required for surgeons obtain FLS certification[38].

"Mini-residency" is another modality of laparoscopic training, usually performed in a 5-d period. Chou *et al*[39] described their experience with 16 participants who had individual didactic sessions with expert faculty and skills-training sessions with inanimate models, pelvic trainers, virtual reality simulators, and the animal and cadaver laboratory. Overall, the participants did not show a statistically significant improvement in their overall laparoscopic skills scores. When subcategories (ring transfer, thread suture, cutting line, suturing) of laparoscopic skills were examined, only the task of threading suture through loops showed a statistically significant improvement after mini-residency. On the follow-up survey, two laparoscopically naive participants had performed laparoscopic nephrectomy, and of the eight participants who had prior renal-ablative laparoscopic experience, four had performed advanced reconstructive laparoscopic cases[39]. In a similar study with 32 participants, Corica *et al*[40] reported their experience with a 5-d mini-residency program that included inanimate model skills training, animal laboratory, and operating room observation. Eight months after mini-residency program, 26 (81%) participants were performing laparoscopic surgery. Compared with before the mini-residency program, laparoscopic radical nephrectomy (P = 0.008), nephroureterectomy (P < 0.0005), and pyeloplasty (P = 0.008) were performed considerably more often by participants after training. Concomitantly, participants performed hand-assisted laparoscopic surgery considerably less often (P = 0.008)[40]. In a large sample including 106 urologists, Kolla *et al*[41] reported similar findings to those described before. In a study evaluating the impact of 5-d mini fellowship program that included tutorial sessions, hands-on inanimate and animate skills training, and clinical case observations, there was also a significant increase in the laparoscopic procedures performed by the participants after the program. Of the surgeons with prior experience with laparoscopy, there was an increase in the practice of laparoscopic radical nephrectomy (88% *vs* 72%), nephroureterectomy (56% *vs* 13%), pyeloplasty (40% *vs* 6%) and partial nephrectomy (32% *vs* 6%). Of the laparoscopic naive surgeons, the take rate was 76%, 52%, 34%, and 32% for laparoscopic radical nephrectomy, nephroureterectomy, pyeloplasty and partial nephrectomy[41]. From all these studies, it is noted that short period training can improve laparoscopic surgical skills, although most of times it is not enough to confer laparoscopic expertise for participants. But one point is clear, short period training is able to increase the laparoscopic practice of surgeons in their communities.

When evaluating the learning process in robot-assisted laparoscopic procedures, the findings are

similar to those described above. One or 2-d courses, as well as mini-fellowship training program, have proved their efficiency of improving participant's robotic skills. Moreover, these courses also are increasing the number of robot-assisted cases performed by the participants in their institutions[42,43].

Full year laparoscopic fellowship programs are another way of improving laparoscopic skills. In a retrospective analysis including more than 4000 surgical cases, the percentage of total cases performed laparoscopically increased from 12.1% to 48.3% after integrating a fellowship-trained surgeon into an established practice. The integration of a fellowship-trained colleague into a general surgery practice resulted in a 300% increase in the proportion of appendectomies, ventral hernias, inguinal hernias, and colectomies performed laparoscopically by the other members of the practice. In this study, when surveyed, the surgeons felt that mentoring by a colleague with laparoscopic training was the most effective method for adopting minimally invasive surgery into their practice[44].

LAPAROSCOPIC TRAINING AND LEARNING CURVE

Sandy *et al*[45] evaluated if laparoscopic skills could be objectively quantified by measuring specific skill parameters during training in a virtual reality surgical simulator. The authors compared the performance of ten medical students with no laparoscopic experience at all with the performance of ten urology residents with some degree of expertise in regards to basic laparoscopic skills, *e.g.,* camera handling, cutting, peg transfer and clipping skills (Immersion Lap VR, San Jose, CA, United States). They found that most individuals in both groups exhibited a significant improvement in their task completion time and error rate, proving that there was a learning curve effect on training. Moreover, the mean time taken to complete tasks was significantly shorter for the urology residents. In addition, this more experienced group of surgeons could complete the tasks with fewer errors. The authors concluded that laparoscopic skills might be objectively measured in a virtual reality surgical simulator based on quantified skill parameters, including the time spent to complete skill tasks and the associated error rate. In a subsequent study from the same group, Duarte *et al*[46] aimed to determine the minimal number of simulator sessions of basic laparoscopic tasks required to elaborate an ideal virtual reality training curriculum. Eleven medical students with no previous laparoscopic experience were enrolled in the study and underwent simulator training sessions starting at level 1, including sequentially camera handling, peg and transfer, clipping and cutting. Each student trained twice a week until a total of ten sessions were completed. By a non-linear regression method analysis, the authors found after 4.26 sessions all students reached the plateau of 80% of the estimated acquired knowledge. From the fifth session till the last, some students could reach 96% of the expected improvement, though the gain of knowledge was not significant.

Training is certainly crucially important for laparoscopic skills learning. However, there are other factors, which should be considered in this equation, and surgeon aptitude is one of this. Buckley *et al*[47] recruited twenty medical students and divided them in two groups according to their aptitude in regards to visual-spatial ability, depth perception, and psychomotor ability. All individuals were tested consecutively using the ProMIS Ⅲ simulator until they reached proficiency performing laparoscopic suturing. Students with high aptitude achieved proficiency after a mean of 7 attempts, ranging from 4 to 10 trials. In converse, only 30% of subjects with low aptitude achieved proficiency after a mean of 14 attempts, ranging from 10 to 16 tries. In addition, in the group with low aptitude, 40% showed improvement but did not reach proficiency, and 30% failed to progress. The authors concluded that the fundamental ability of distinguish individuals lead to distinct learning curves for laparoscopic suturing, where high aptitude is directly related to earlier completion of the learning curve.

Another factor that has been proved to influence on the learning curve for laparoscopic training is coaching[48,49]. Cole *et al*[48] compared the effects of structured coaching with an autodidactic training in simulated laparoscopic surgery. Seventeen surgically inexperienced medical students were randomized into two groups, eight being placed into an intervention group which received structured coaching, and nine being placed into a control group who received no training at all. All subjects performed ten laparoscopic cholecystectomies on a virtual reality simulator and the surgical quality of the first, fifth, and tenth operations was evaluated by two independent blinded assessors using the competency assessment tool (CAT) for cholecystectomy. They found that the coached group scored significantly higher on the CAT assessment and knowledge test of procedures one, five, and ten, with increasing disparity. The learning curve for error frequency of the coached group reached competency after operation seven, while the control group did not plateau by the last procedure. The authors concluded that structured coaching might represent a key element in the acquisition of laparoscopic surgical skills. In the same sense, Ahlberg *et al*[49] evaluated individual learning curves for a cohort of surgeons performing laparoscopic fundoplication and analyzed if the Procedicus MIST-simulator (Mentice Inc., Göteborg, Sweden) could predict surgical performance. For that, twelve centers participated and each contributed with a "master" and a "pupil" surgeon. Pupils were tested in the simulator and then performed their first twenty supervised operations. All procedures were recorded

and thereafter appraised by three independent reviewers. The authors found the master to significantly affect the pupil's score and concluded that Individual learning curves varied, and the teacher was shown to be the most important factor influencing the pupil's performance score.

More recently, a technological advancement allowed for a shorter learning curve during laparoscopic training. Romero-Loera *et al*[50] tested the potential benefit of in-depth perception of 3D images in laparoscopic surgery. They recruited 40 individuals with no experience in laparoscopic surgery and divided them in two groups: 20 began the skills in the 2D modality and then performed them in 3D, and the other 20 began in 3D and then shifted to 2D. Each subject was used as his own control. Of all skills evaluated, there was a significantly difference in time improvement between groups, being 72% in the 3D group compared to 37% in the 2D modality. In addition, the accomplishment percentage using the 3D laparoscopy was greater for both groups. Finally, subjects' preference was also evaluated and 52.5% of participants preferred 3D laparoscopy, only 15% preferred 2D, and 32.5% had no preferences. The authors concluded that 3D laparoscopic surgical training is feasible and superior to 2D, with a shorter learning curve.

Finally, the learning curve has a potential benefit in terms of cost-savings. Stefanidis *et al*[51] compared a group of ten medical students who trained until proficiency was achieved on five basic laparoscopic tasks with a group of ten students who received no training. After this initial step, both groups underwent a supervised training on the Fundamentals of Laparoscopic Surgery suturing model until previously reported proficiency levels were achieved and then two weeks later they were retested to evaluate their retention scores, training parameters, instruction requirements, and cost between groups. The initial performance on the simulator was better for individual with basic skills training, their suturing learning curve was shorter, and they required less active instruction. Although the overall time required to finish the curriculum was similar for both cohorts, the subjects who underwent a previous training strategy cost less, with mean savings of USD148 per student. Therefore, they determined that teaching novices basic laparoscopic skills before a more complex laparoscopic task allows substantial cost savings.

CONCLUSION

Laparoscopic surgery has been replacing the open standard technique in several procedures. However, the learning curve required to obtain laparoscopic expertise has been an issue in medical community. Laparoscopic surgery training laboratory was developed to overcome this barrier. Although a short period of training can improve laparoscopic surgical skills, full laparoscopic training in medical residence or fellowship program is the best way of stimulating laparoscopic dissemination.

REFERENCES

1 **Coccolini F**, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, Leandro G, Montori G, Ceresoli M, Corbella D, Sartelli M, Sugrue M, Ansaloni L. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. *Int J Surg* 2015; **18**: 196-204 [PMID: 25958296 DOI: 10.1016/j.ijsu.2015.04.083]

2 **Li X**, Zhang J, Sang L, Zhang W, Chu Z, Li X, Liu Y. Laparoscopic versus conventional appendectomy--a meta-analysis of randomized controlled trials. *BMC Gastroenterol* 2010; **10**: 129 [PMID: 21047410 DOI: 10.1186/1471-230X-10-129]

3 **Sammour T**, Jones IT, Gibbs P, Chandra R, Steel MC, Shedda SM, Croxford M, Faragher I, Hayes IP, Hastie IA. Comparing oncological outcomes of laparoscopic versus open surgery for colon cancer: Analysis of a large prospective clinical database. *J Surg Oncol* 2015; **111**: 891-898 [PMID: 25712421 DOI: 10.1002/jso.23893]

4 **Mei H**, Pu J, Yang C, Zhang H, Zheng L, Tong Q. Laparoscopic versus open pyeloplasty for ureteropelvic junction obstruction in children: a systematic review and meta-analysis. *J Endourol* 2011; **25**: 727-736 [PMID: 21476861 DOI: 10.1089/end.2010.0544]

5 **Laird A**, Choy KC, Delaney H, Cutress ML, O'Connor KM, Tolley DA, McNeill SA, Stewart GD, Riddick AC. Matched pair analysis of laparoscopic versus open radical nephrectomy for the treatment of T3 renal cell carcinoma. *World J Urol* 2015; **33**: 25-32 [PMID: 24647880 DOI: 10.1007/s00345-014-1280-y]

6 **Hung AJ**, Zehnder P, Patil MB, Cai J, Ng CK, Aron M, Gill IS, Desai MM. Face, content and construct validity of a novel robotic surgery simulator. *J Urol* 2011; **186**: 1019-1024 [PMID: 21784469 DOI: 10.1016/j.juro.2011.04.064]

7 **Fried GM**, Feldman LS, Vassiliou MC, Fraser SA, Stanbridge D, Ghitulescu G, Andrew CG. Proving the value of simulation in laparoscopic surgery. *Ann Surg* 2004; **240**: 518-525; discussion 525-528 [PMID: 15319723]

8 **Derossis AM**, Bothwell J, Sigman HH, Fried GM. The effect of practice on performance in a laparoscopic simulator. *Surg Endosc* 1998; **12**: 1117-1120 [PMID: 9716763]

9 **Muresan C**, Lee TH, Seagull J, Park AE. Transfer of training in the development of intracorporeal suturing skill in medical student novices: a prospective randomized trial. *Am J Surg* 2010; **200**: 537-541 [PMID: 20451174 DOI: 10.1016/j.amjsurg.2009.12.018]

10 **Korndorffer JR**, Hayes DJ, Dunne JB, Sierra R, Touchard CL, Markert RJ, Scott DJ. Development and transferability of a cost-effective laparoscopic camera navigation simulator. *Surg Endosc* 2005; **19**: 161-167 [PMID: 15624054 DOI: 10.1007/s00464-004-8901-2]

11 **Mulla M**, Sharma D, Moghul M, Kailani O, Dockery J, Ayis S, Grange P. Learning basic laparoscopic skills: a randomized controlled study comparing box trainer, virtual reality simulator, and mental training. *J Surg Educ* 2012; **69**: 190-195 [PMID: 22365864 DOI: 10.1016/j.jsurg.2011.07.011]

12 **Munz Y**, Kumar BD, Moorthy K, Bann S, Darzi A. Laparoscopic virtual reality and box trainers: is one superior to the other? *Surg Endosc* 2004; **18**: 485-494 [PMID: 14752633 DOI: 10.1007/s00464-003-9043-7]

13 **Torkington J**, Smith SG, Rees BI, Darzi A. Skill transfer from virtual reality to a real laparoscopic task. *Surg Endosc* 2001; **15**: 1076-1079 [PMID: 11727073 DOI: 10.1007/s004640000233]

14 **Jordan JA**, Gallagher AG, McGuigan J, McClure N. Virtual reality training leads to faster adaptation to the novel psychomotor restrictions encountered by laparoscopic surgeons. *Surg Endosc* 2001; **15**: 1080-1084 [PMID: 11727074 DOI: 10.1007/s004640000374]

15 **Nagendran M**, Toon CD, Davidson BR, Gurusamy KS. Laparoscopic surgical box model training for surgical trainees with no prior laparoscopic experience. *Cochrane Database Syst Rev* 2014; **(1)**: CD010479 [PMID: 24442763 DOI: 10.1002/14651858.CD010479.pub2]

16 **Schreuder HW**, van Dongen KW, Roeleveld SJ, Schijven MP, Broeders IA. Face and construct validity of virtual reality simulation of laparoscopic gynecologic surgery. *Am J Obstet Gynecol* 2009; **200**: 540.e1-540.e8 [PMID: 19285646 DOI: 10.1016/

j.ajog.2008.12.030]
17 **Sánchez-Peralta LF**, Sánchez-Margallo FM, Moyano-Cuevas JL, Pagador JB, Enciso-Sanz S, Sánchez-González P, Gómez-Aguilera EJ, Usón-Gargallo J. Construct and face validity of SINERGIA laparoscopic virtual reality simulator. *Int J Comput Assist Radiol Surg* 2010; **5**: 307-315 [PMID: 20422300 DOI: 10.1007/s11548-010-0425-8]
18 **Torricelli FC**, Guglielmetti G, Duarte RJ, Srougi M. Laparoscopic skill laboratory in urological surgery: tools and methods for resident training. *Int Braz J Urol* 2011; **37**: 108-111; discussion 112 [PMID: 21385487]
19 **Ikonen TS**, Antikainen T, Silvennoinen M, Isojärvi J, Mäkinen E, Scheinin TM. Virtual reality simulator training of laparoscopic cholecystectomies - a systematic review. *Scand J Surg* 2012; **101**: 5-12 [PMID: 22414461]
20 **Madan AK**, Frantzides CT. Prospective randomized controlled trial of laparoscopic trainers for basic laparoscopic skills acquisition. *Surg Endosc* 2007; **21**: 209-213 [PMID: 17122975 DOI: 10.1007/s00464-006-0149-6]
21 **Nagendran M**, Gurusamy KS, Aggarwal R, Loizidou M, Davidson BR. Virtual reality training for surgical trainees in laparoscopic surgery. *Cochrane Database Syst Rev* 2013; **(8)**: CD006575 [PMID: 23980026 DOI: 10.1002/14651858.CD006575.pub3]
22 **Gavazzi A**, Bahsoun AN, Van Haute W, Ahmed K, Elhage O, Jaye P, Khan MS, Dasgupta P. Face, content and construct validity of a virtual reality simulator for robotic surgery (SEP Robot). *Ann R Coll Surg Engl* 2011; **93**: 152-156 [PMID: 22041146 DOI: 10.1308/003588411X12851639108358]
23 **Lee JY**, Mucksavage P, Kerbl DC, Huynh VB, Etafy M, McDougall EM. Validation study of a virtual reality robotic simulator--role as an assessment tool? *J Urol* 2012; **187**: 998-1002 [PMID: 22264455 DOI: 10.1016/j.juro.2011.10.160]
24 **Moglia A**, Ferrari V, Morelli L, Ferrari M, Mosca F, Cuschieri A. A Systematic Review of Virtual Reality Simulators for Robot-assisted Surgery. *Eur Urol* 2016; **69**: 1065-1080 [PMID: 26433570 DOI: 10.1016/j.eururo.2015.09.021]
25 **La Torre M**, Caruso C. The animal model in advanced laparoscopy resident training. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 271-275 [PMID: 23751991 DOI: 10.1097/SLE.0b013e31828b895b]
26 **Palter VN**, Orzech N, Aggarwal R, Okrainec A, Grantcharov TP. Resident perceptions of advanced laparoscopic skills training. *Surg Endosc* 2010; **24**: 2830-2834 [PMID: 20428895 DOI: 10.1007/s00464-010-1058-2]
27 **La Torre M**, Caruso C. Resident training in laparoscopic colorectal surgery: role of the porcine model. *World J Surg* 2012; **36**: 2015-2020 [PMID: 22689021 DOI: 10.1007/s00268-012-1675-0]
28 **Zimmerman H**, Latifi R, Dehdashti B, Ong E, Jie T, Galvani C, Waer A, Wynne J, Biffar D, Gruessner R. Intensive laparoscopic training course for surgical residents: program description, initial results, and requirements. *Surg Endosc* 2011; **25**: 3636-3641 [PMID: 21643881 DOI: 10.1007/s00464-011-1770-6]
29 **Rassweiler J**, Henkel TO, Potempa DM, Coptcoat MJ, Miller K, Preminger GM, Alken P. Transperitoneal laparoscopic nephrectomy: training, technique, and results. *J Endourol* 1993; **7**: 505-515; discussion 515-516 [PMID: 8124347]
30 **Ganpule A**, Chhabra JS, Desai M. Chicken and porcine models for training in laparoscopy and robotics. *Curr Opin Urol* 2015; **25**: 158-162 [PMID: 25581541 DOI: 10.1097/MOU.0000000000000139]
31 **Cicione A**, Autorino R, Laguna MP, De Sio M, Micali S, Turna B, Sanchez-Salas R, Quattrone C, Dias E, Mota P, Bianchi G, Damano R, Rassweiler J, Lima E. Three-dimensional Technology Facilitates Surgical Performance of Novice Laparoscopy Surgeons: A Quantitative Assessment on a Porcine Kidney Model. *Urology* 2015; **85**: 1252-1256 [PMID: 26099869 DOI: 10.1016/j.urology.2015.03.009]
32 **Korndorffer JR**, Stefanidis D, Scott DJ. Laparoscopic skills laboratories: current assessment and a call for resident training standards. *Am J Surg* 2006; **191**: 17-22 [PMID: 16399100 DOI: 10.1016/j.amjsurg.2005.05.048]
33 **Bjerrum F**, Sorensen JL, Thinggaard J, Strandbygaard J, Konge L. Implementation of a Cross-specialty Training Program in Basic Laparoscopy. *JSLS* 2015; **19**: pii: e2015.00059 [PMID: 26527858 DOI: 10.4293/JSLS.2015.00059]
34 **Nelson K**, Bagnall A, Nesbitt C, Davey P, Mafeld S. Developing cross-specialty endovascular simulation training. *Clin Teach* 2014; **11**: 411-415 [PMID: 25212923 DOI: 10.1111/tct.12174]
35 **Lund L**, Høj L, Poulsen J, Funch-Jensen P, Nilsson T. Organisation of basic training in laparoscopic surgery. *Ugeskr Laeger* 2010; **172**: 436-440 [PMID: 20146906]
36 **Asano TK**, Soto C, Poulin EC, Mamazza J, Boushey RP. Assessing the impact of a 2-day laparoscopic intestinal workshop. *Can J Surg* 2011; **54**: 223-226 [PMID: 21651832 DOI: 10.1503/cjs.005310]
37 **Peters JH**, Fried GM, Swanstrom LL, Soper NJ, Sillin LF, Schirmer B, Hoffman K. Development and validation of a comprehensive program of education and assessment of the basic fundamentals of laparoscopic surgery. *Surgery* 2004; **135**: 21-27 [PMID: 14694297 DOI: 10.1016/S0039]
38 **Okrainec A**, Smith L, Azzie G. Surgical simulation in Africa: the feasibility and impact of a 3-day fundamentals of laparoscopic surgery course. *Surg Endosc* 2009; **23**: 2493-2498 [PMID: 19343438 DOI: 10.1007/s00464-009-0424-4]
39 **Chou DS**, Abdelshehid CS, Uribe CA, Khonsari SS, Eichel L, Boker JR, Shanberg AM, Ahlering TE, Clayman RV, McDougall EM. Initial impact of a dedicated postgraduate laparoscopic mini-residency on clinical practice patterns. *J Endourol* 2005; **19**: 360-365 [PMID: 15865528 DOI: 10.1089/end.2005.19.360]
40 **Corica FA**, Boker JR, Chou DS, White SM, Abdelshehid CS, Stoliar G, Sala LG, Shanberg AM, Clayman RV, McDougall EM. Short-term impact of a laparoscopic "mini-residency" experience on postgraduate urologists' practice patterns. *J Am Coll Surg* 2006; **203**: 692-698 [PMID: 17084331 DOI: 10.1016/j.jamcollsurg.2006.07.027]
41 **Kolla SB**, Gamboa AJ, Li R, Santos RT, Gan JM, Shell C, Andrade L, Louie MK, Clayman RV, McDougall EM. Impact of a laparoscopic renal surgery mini-fellowship program on postgraduate urologist practice patterns at 3-year followup. *J Urol* 2010; **184**: 2089-2093 [PMID: 20850830 DOI: 10.1016/j.juro.2010.06.097]
42 **Gamboa AJ**, Santos RT, Sargent ER, Louie MK, Box GN, Sohn KH, Truong H, Lin R, Khosravi A, Santos R, Ornstein DK, Ahlering TE, Tyson DR, Clayman RV, McDougall EM. Long-term impact of a robot assisted laparoscopic prostatectomy mini fellowship training program on postgraduate urological practice patterns. *J Urol* 2009; **181**: 778-782 [PMID: 19091351 DOI: 10.1016/j.juro.2008.10.018]
43 **Altunrende F**, Autorino R, Haber GP, Laydner H, White MA, Khanna R, Stein RJ, Kaouk JH. Immediate impact of a robotic kidney surgery course on attendees practice patterns. *Int J Med Robot* 2011; **7**: 165-169 [PMID: 21472968 DOI: 10.1002/rcs.384]
44 **Dominguez EP**, Barrat C, Shaffer L, Gruner R, Whisler D, Taylor P. Minimally invasive surgery adoption into an established surgical practice: impact of a fellowship-trained colleague. *Surg Endosc* 2013; **27**: 1267-1272 [PMID: 23232996 DOI: 10.1007/s00464-012-2594-8]
45 **Sandy NS**, Cruz JA, Passerotti CC, Nguyen H, Reis ST, Gouveia EM, Duarte RJ, Bruschini H, Srougi M. Can the learning of laparoscopic skills be quantified by the measurements of skill parameters performed in a virtual reality simulator? *Int Braz J Urol* 2013; **39**: 371-376 [PMID: 23849568 DOI: 10.1590/S1677-5538.IBJU.2013.03.10]
46 **Duarte RJ**, Cury J, Oliveira LC, Srougi M. Establishing the minimal number of virtual reality simulator training sessions necessary to develop basic laparoscopic skills competence: evaluation of the learning curve. *Int Braz J Urol* 2013; **39**: 712-719 [PMID: 24267114 DOI: 10.1590/S1677-5538.IBJU.2013.05.14]
47 **Buckley CE**, Kavanagh DO, Nugent E, Ryan D, Traynor OJ, Neary PC. The impact of aptitude on the learning curve for laparoscopic suturing. *Am J Surg* 2014; **207**: 263-270 [PMID: 24468026 DOI: 10.1016/j.amjsurg.2013.08.037]
48 **Cole SJ**, Mackenzie H, Ha J, Hanna GB, Miskovic D. Randomized controlled trial on the effect of coaching in simulated laparoscopic training. *Surg Endosc* 2014; **28**: 979-986 [PMID: 24196554 DOI: 10.1007/s00464-013-3265-0]
49 **Ahlberg G**, Kruuna O, Leijonmarck CE, Ovaska J, Rosseland A,

Sandbu R, Strömberg C, Arvidsson D. Is the learning curve for laparoscopic fundoplication determined by the teacher or the pupil? *Am J Surg* 2005; **189**: 184-189 [PMID: 15720987 DOI: 10.1016/j.amjsurg.2004.06.043]

50 **Romero-Loera S**, Cárdenas-Lailson LE, de la Concha-Bermejillo F, Crisanto-Campos BA, Valenzuela-Salazar C, Moreno-Portillo M. Skills comparison using a 2D vs. 3D laparoscopic simulator. *Cir Cir* 2016; **84**: 37-44 [PMID: 26259739 DOI: 10.1016/j.circir.2015.06.032]

51 **Stefanidis D**, Hope WW, Korndorffer JR, Markley S, Scott DJ. Initial laparoscopic basic skills training shortens the learning curve of laparoscopic suturing and is cost-effective. *J Am Coll Surg* 2010; **210**: 436-440 [PMID: 20347735 DOI: 10.1016/j.jamcollsurg.2009.12.015]

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SYSTEMATIC REVIEWS

Critical analysis of the literature investigating urogenital function preservation following robotic rectal cancer surgery

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Abstract

AIM

To analyses the current literature regarding the urogenital functional outcomes of patients receiving robotic rectal cancer surgery.

METHODS

A comprehensive literature search of electronic databases was performed in October 2015. The following search terms were applied: "rectal cancer" or "colorectal cancer" and robot* or "da Vinci" and sexual or urolog* or urinary or erect* or ejaculat* or impot* or incontinence. All original studies examining the urological and/or sexual outcomes of male and/or female patients receiving robotic rectal cancer surgery were included. Reference lists of all retrieved articles were manually searched for further relevant articles. Abstracts were independently searched by two authors.

RESULTS

Fifteen original studies fulfilled the inclusion criteria. A total of 1338 patients were included; 818 received robotic, 498 laparoscopic and 22 open rectal cancer surgery. Only 726 (54%) patients had their urogenital function assessed *via* means of validated functional questionnaires. From the included studies, three found that robotic rectal cancer surgery leads to quicker recovery of male urological function and five of male sexual function as compared to laparoscopic surgery. It is unclear whether robotic surgery offers favourable urogenital outcomes in the long run for males. In female patients only two studies assessed urological and three

sexual function independently to that of males. In these studies there was no difference identified between patients receiving robotic and laparoscopic rectal cancer surgery. However, in females the presented evidence was very limited making it impossible to draw any substantial conclusions.

CONCLUSION

There seems to be a trend towards earlier recovery of male urogenital function following robotic surgery. To evaluate this further, larger well designed studies are required.

Key words: Rectal neoplasms; Robotic surgical procedures; Colorectal surgery; Sexual dysfunction; Physiological; Urinary bladder; Neurogenic; Humans

Core tip: Urogenital dysfunction is a significant problem following rectal cancer surgery that significantly affects quality of life. Despite laparoscopic total mesorectal excision becoming the standard approach in much of the developed world, the incidence of post-operative urogenital dysfunction remains high. Robotic surgery allows for precision surgery in the pelvis, therefore enabling better preservation of the pelvic autonomic nerves. Current studies examining the urogenital outcomes following robotic rectal cancer surgery have several limitations, but suggest that robotic surgery may offer favourable outcomes when compared to laparoscopic and open surgery. Larger scale prospective studies are required to validate these results.

Panteleimonitis S, Ahmed J, Harper M, Parvaiz A. Critical analysis of the literature investigating urogenital function preservation following robotic rectal cancer surgery. *World J Gastrointest Surg* 2016; 8(11): 744-754 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i11/744.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i11.744

INTRODUCTION

Colorectal cancer is one of the most common cancers in the developed world[1-3] with rectal cancers making up a third of those cancers[2-4]. The aim of rectal cancer surgery is to radically resect the cancer in order to achieve oncological cure and avoid local recurrence. During the past three decades significant improvements have been made to combat this predicament. These advances include earlier diagnosis, advanced surgical techniques and the improvement of adjuvant and neoadjuvant treatment[4-8]. These developments were not only aimed to improve the patients' survival but also directed to improve the quality of life after cancer rectal surgery.

Urogenital function is one of the most important aspects of quality of life and rectal cancer may have adverse effects on it[5,9-13]. Although urogenital dysfunction is considered to be multifactorial, intra-operative damage to the pelvic autonomic nerves is the primary cause[14-16]. This is mainly due to the close proximity of the mesorectum to the autonomic nerves, and the difficulty in identifying such small structures such as the autonomic nerves in a narrow operative space such as the pelvis[13,17]. Damage to the sympathetic nerves results in urinary incontinence, ejaculation disorders in men and decreased orgasmic intensity in women[13,18]. Damage to the parasympathetic nerves leads to a lack of detrusor muscle function and subsequent voiding disorder, as well as erectile problems and lubrication dysfunction in men and women respectively[13,18]. These are significant post-operative and life changing events that jeopardise patients quality of life[9].

It is logical to assume that better visualisation of the structures of the pelvis, such as offered from laparoscopic or robotic surgery, can aid preservation of the autonomic nerves. Nevertheless, there is a debate as to whether laparoscopic surgery offers improved urogenital functional outcomes when compared to open surgery[19], as some studies have shown improved outcomes[20] while other advocate the contrary[21]. A probable reason for the disparate results is due to laparoscopic rectal surgery being technically difficult[22], as evident from its long learning curve[23] and the high conversion rate demonstrated in the CLASSICC and COLOR Ⅱ trials[24,25]. Existing laparoscopic instruments have a restricted range of movement compared with that of the surgeons hand and are difficult to use in confined spaces such as the pelvis[26,27].

Robotic surgical systems were introduced to overcome the technical limitations of laparoscopic surgery[28]. They provide a superior three dimensional view, tremor filtering and superior ergonomic instrumentation[26,29]. These chattels enable precise dissection in narrow surgical fields such as the pelvis and help preserve the autonomic nerves. Even though multiple studies have examined the pathological, oncological and postoperative outcomes of robotic rectal surgery, there are only a few studies that have investigated the urological and sexual outcomes of robotic rectal cancer surgery and these tend to be predominantly about male patients.

Therefore the aim of this systematic review is to examine the available literature on the postoperative urogenital outcomes of robotic rectal cancer surgery on both male and female patients.

MATERIALS AND METHODS

A comprehensive literature search of electronic databases was performed in October 2015 by using the Discovery search engine tool (for more info refer to: http://www.port.ac.uk/library/infores/discovery/). Discovery is Portsmouth University's search engine tool and it simultaneously searches over 200 scientific

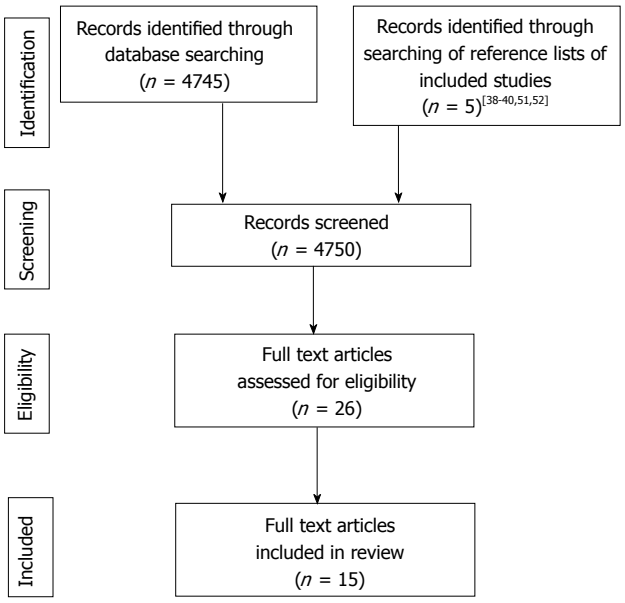

Figure 1 Selection process flow diagram.

electronic databases including MEDLINE (PubMed), Google Scholar and Science Direct. The following search terms were applied: "rectal cancer" or "colorectal cancer" and robot* or "da Vinci" and sexual or urolog* or urinary or erect* or ejaculat* or impot* or incontinence. All original studies that reported the urological and/or sexual outcomes of patients having robotic rectal cancer surgery were included. Reference lists of all retrieved articles were manually searched for further relevant articles. A flow diagram of the selection process is given in Figure 1. Abstracts were independently searched by two authors. Fifteen full text articles fulfilled the inclusion criteria.

RESULTS

Original studies

A total of 1338 patients were included in the reviewed studies (818 received robotic, 498 laparoscopic and 22 open rectal cancer surgery). The characteristics of all the original studies reporting either urinary or sexual outcomes are outlined in Tables 1 and 2. Of the 15 studies that met the inclusion criteria, 14 were cohort studies[5,6,9,18,30-39] and one a randomised control trial[40]. Nine of the cohort studies were comparing robotic rectal cancer surgery to either laparoscopic[9,30-33,35,38,40] or open[18] rectal cancer surgery.

Out of the 15 studies only six[5,6,9,18,30,31] were specific to urogenital outcomes; the rest reported urogenital outcomes amongst a multitude of outcomes examined in those studies.

Outcome assessment

Functional questionnaire scores were used in ten[5,6,9,18,30-33,36,37] of these studies to access the urological and sexual function of patients. These questionnaires are validated tools that have been used in a multitude of previous studies to access urinary and sexual function in males and females[41-45]. Out of the 1338 patients included in this review, only 726 (54%; 442 robotic, 262 laparoscopic, 22 open) had their urogenital function assessed *via* functional questionnaires.

To assess male urological function the majority of studies used the International Prostatic Symptoms Score (IPSS) or a slight modification of it. This is a subjective scoring system examining seven categories[41]. These include incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. Patients score each category and assign a higher score for increasing severity of symptoms. Alternative questionnaires used to assess urological function were the the International Consultation on Incontinence Questionnaire - Male Lower Urinary Tract Symptoms[44], and the International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms[45] questionnaire.

Male sexual function was assessed in ten studies by the international index of erectile function (IIEF)[42] score. The IIEF is a 15-item score that analyses five factors: Erectile function, orgasmic function, libido, intercourse satisfaction and overall satisfaction. Unlike the IPSS score for urinary function, a high IIEF score is associated with good sexual function and the lower the IIEF score the greater the degree of sexual dysfunction.

Female sexual function was assessed in three studies[6,30,37] *via* the Female Sexual Function Index (FSFI)[43]. This is a validated questionnaire that is in many ways the female version of the IIEF questionnaire.

The studies that did not use validated scoring tools to assess functional outcomes simply reported the incidence of dysfunction. The limitations present in this method of reporting are the inability to quantify dysfunction and the difficulty in defining what makes a case.

Finally, one study[31] assessed urological function by performing urodynamic studies as well as using a validated functional questionnaire, making it the only study to report urinary outcomes with both subjective and objective measurement tools.

Pre-operative assessment and follow up

The studies assessing functional outcomes *via* validated questionnaires asked their participants to fill the questionnaires pre-operatively in order to establish their baseline urogenital function. In this way post-operative scores were assessed against the pre-operative scores for each patient, allowing the change of function from baseline to be assessed. Reporting the change of function from baseline is a more accurate way of assessing the impact of the intervention, rather than reporting the postoperative functional scores alone.

It was unclear across several of the studies[6,18,30,32] how many patients were sexually inactive pre-operatively and whether they were included in the analysis. Adding sexually inactive patients in the analysis will result in skewing of the data and it is therefore important

Table 1 Characteristics of original studies

Ref.	Country	Study design	Control group	No. of cases for urogenital outcomes	Study specifically examines urogenital outcomes
Hellan *et al*[34]	United States	Retrospective	No control group	39	No
Patriti *et al*[40]	Italy	RCT	Robot *vs* lap	29 rob *vs* 37 lap	No
Luca *et al*[6]	Italy	Prospective	No control group	74	Yes
Kim *et al*[31]	South Korea	Prospective	Robot *vs* lap	30 rob *vs* 39 lap	Yes
Park *et al*[39]	United States	Prospective	No control group	30	No
Leung *et al*[5]	Hong Kong	Prospective	No control group	33	Yes
Park *et al*[32]	South Korea	Retrospective	Robot *vs* lap	14 rob *vs* 15 lap	No
D'Annibale *et al*[33]	Italy	Retrospective	Robot *vs* lap	30 *vs* 30	No
Stănciulea *et al*[37]	Romania	Retrospective	No control group	78	No
Erguner *et al*[38]	Turkey	Prospective	Robot *vs* lap	27 rob *vs* 37 lap	No
Park *et al*[9]	South Korea	Retrospective	Robot *vs* lap	32 *vs* 32	Yes
Ozeki *et al*[18]	Japan	Prospective	Robot *vs* open	15 rob *vs* 22 open	Yes
Cho *et al*[35]	South Korea	Retrospective	Robot *vs* lap	278 *vs* 278	No
Alecu *et al*[36]	Romania	Retrospective	No control group	79	No
Morelli *et al*[30]	Italy	Retrospective	Robot *vs* lap	30 *vs* 30	Yes

These include: (1) the studies country of origin; (2) the study design (prospective, retrospective or randomised control trial); (3) the control group (if present) used to compare with the robotic rectal surgery, this was either laparoscopic or open rectal surgery cases; (4) the number of cases included in each study whose urogenital outcomes were evaluated; and (5) whether the study was specifically designed to investigate the urogenital outcomes of robotic surgery or not. RCT: Randomised control trial; Robot: Robotic; lap: Laparoscopic.

to report how many patients were sexually inactive and whether they were included in the analysis or not.

In contrast to the studies applying validated functional scores, most of the studies that simply reported the incidence of urogenital dysfunction did not mention the pre-operative state of their participants. This makes it difficult to assess whether any cases of dysfunction became cases because of the intervention or not.

Follow up was fairly variable between the different studies and the follow up intervals for each study are summarised in Table 2. The majority of the studies followed up their patients in more than one occasion following surgery. The commonest follow up intervals were 3, 6 and 12 mo post-operatively.

Quality of included original studies

The Scottish Intercollegiate Guidelines Network critical appraisal tool for cohort studies was used to evaluate the original studies included in this review. However, none of the studies met the majority of the criteria for a high quality study. Most of the studies fell between the acceptable and low quality bracket (Table 2). The majority of studies were retrospective in nature, included a small number of patients, were subject to selection bias in terms of patient selection and made no adjustments for confounding factors.

The studies included in this review have significant differences in terms of outcome reporting and methodology. In addition, almost all of them are non-randomised in nature. Considering this and because of the heterogeneity of the data in these studies it was not appropriate to perform a meta-analysis. There are only a few studies whose data were homogeneous enough to permit a meta-analysis. However, this has already been performed by two previous systematic reviews[46,47] which combined the data of three studies. We discuss these systematic reviews in our discussion.

Male urological function

Out of the 15 original studies included, 12 studies reported male urological functional outcomes. The characteristics of these studies plus a summary of their results are present in Table 3.

Validated functional scores were used in nine of the above studies. Six of those compared the scores of patients undergoing robotic surgery with those undergoing laparoscopic or open surgery. Most studies[18,30,32,33] showed that urological function tended to deteriorate in the early postoperative phase (1-3 mo) but later recovered with time (6-12 mo) irrespective of surgical modality. One study[9] found that IPSS score change from baseline was less in the robotic group at 12 mo after surgery, but failed to reach statistical significance ($P = 0.051$).

Kim *et al*[31] reported IPSS scores in favour of the robotic group. They found that IPSS scores significantly increased 1 mo after surgery; but then recovered in 3 mo in the robotic group and 6 mo in the laparoscopic group with a statistically significant lesser deterioration of scores from baseline in the 3 mo follow up period in the robotic group ($P = 0.036$). It is worth noting that Kim *et al*[31]'s study was the only one to assess urinary function by means of urodynamic studies in conjunction with a functional score. He reported that the deterioration in mean voiding volume from baseline was statistically less in 3 and 6 mo post-op in favour of the robotic group ($P = 0.007$, $P = 0.049$). The only other study to report urological outcomes in favour of the robotic group was Cho *et al*[35]'s study; reporting a higher voiding dysfunction rate in the laparoscopic group (4.3% *vs* 0.7%; $P = 0.012$). However, this study did not use any functional scores to assess urological function.

Female urological function

Seven studies reported female urological functional

Table 2 Further characteristics of original studies

Ref.	Fully or hybrid robotic procedure	Functional scores applied	Follow up in months	No. of surgeons performing cases	SIGN score
Hellan *et al*[34]	Hybrid	No	Median f/u 13 mo	Not stated	+
Patriti *et al*[40]	Hybrid	No	Mean f/u 12 mo	Not stated	+
Luca *et al*[6]	Fully	Yes	1, 6, 12	2 surgeons	++
Kim *et al*[31]	Hybrid	Yes	1, 3, 6, 12	1 surgeon	++
Park *et al*[39]	Reverse hybrid	No	Not stated	Not stated	+
Leung *et al*[5]	Mixture	Yes	3	Not stated	++
Park *et al*[32]	Hybrid	Yes	3, 6, 12	1 surgeon	++
D'Annibale *et al*[33]	Fully	Yes	1, 12	1 surgeon	++
Stănciulea *et al*[37]	93% fully	Yes	Once b/n 6 and 12 mo	3 surgeons	+
Erguner *et al*[38]	Mixture	No	Not stated	Not stated	+
Park *et al*[9]	Hybrid	Yes	3, 6, 12	1 surgeon	++
Ozeki *et al*[18]	Fully	Yes	3, 6, 12	2 for robot cases	++
Cho *et al*[35]	Fully	No	1	3 surgeons did 97.1% cases	++
Alecu *et al*[36]	Hybrid	Yes	Not stated	Not stated	+
Morelli *et al*[30]	Not stated	Yes	1, 6, 12	1 surgeon	++

These include: (1) whether the surgeons used the hybrid or robotic approach for their study; (2) whether urogenital function was assessed by means of functional scores or not; (3) the follow up period during which data for urogenital outcomes was collected; (4) the number of surgeons performing the cases in each study; and (5) the studies SIGN score. f/u: Follow up; SIGN: Scottish Intercollegiate Guidelines Network.

Table 3 Original studies reporting male urological function

Ref.	Males assessed independently of females	Functional scores applied	Control group	No. of cases examining male urological function	Follow up in months	Outcome summary
Kim *et al*[31]	No	Yes	Robot *vs* lap	30 rob *vs* 39 lap	1, 3, 6, 12	Urological function recovered faster in robotic group (3 mo *vs* 6 mo) IPSS change from baseline lower in robotic group at 3 mo (P = 0.036) Mean voiding volume deterioration lower in 3 and 6 mo in robotic group (P = 0.007, P = 0.049) Similar outcomes at 12 mo in both groups
Park *et al*[9]	Yes	Yes	Robot *vs* lap	32 *vs* 32	3, 6, 12	IPSS scores elevated post-operatively in both groups At 12 mo IPSS change from baseline lower in robotic group but non-significant (P = 0.051)
Park *et al*[32]	Yes	Yes	Robot *vs* lap	14 rob *vs* 15 lap	3, 6, 12	Deterioration of IPSS scores in 3 mo which recovered by 6 mo in both groups
D'Annibale *et al*[33]	Yes	Yes	Robot *vs* lap	30 *vs* 30	1, 12	Deterioration of IPSS scores in 3 mo which recovered by 12 mo in both groups
Ozeki *et al*[18]	Yes	Yes	Robot *vs* open	15 rob *vs* 22 open	3, 6, 12	No statistical deterioration of IPSS scores in either group
Morelli *et al*[30]	Yes	Yes	Robot *vs* lap	Not available	1, 6, 12	Voiding and incontinence worse 1 mo in both groups, incontinence recovered by 6-12 mo in both groups
Leung *et al*[5]	Yes	Yes	No control group	33	3	No significant male urological function deterioration
Luca *et al*[6]	Yes	Yes	No control group	38	1, 6, 12	No significant male urological function deterioration
Stănciulea *et al*[37]	No	Yes	No control group	78	Once b/n 6 and 12	No deterioration in IPSS scores but no data presentation in results
Hellan *et al*[34]	No	No	No control group	39	median F/U 13 mo	One patient (2.56%) developed bladder dysfunction post operatively
Park *et al*[39]	No	No	No control group	30	Not stated	No patients developed bladder dysfunction post operatively
Cho *et al*[35]	No	No	Robot *vs* lap	278 *vs* 278	1	Voiding dysfunction rate higher in the laparoscopic group (4.3% lap *vs* 0.7% rob; P = 0.012)

The following study characteristics are described: (1) whether male patients were assessed independently of female patients or not, in studies that this was not the case data from male and female patients was combined; (2) whether functional scores were used to assess urogenital outcomes or not; (3) the control group used in the study if applicable; (4) the number of cases examining male urological function; (4) the follow up periods in months; and (5) a brief summary of the study's findings regarding male urological function. Robot: Robotic; lap: Laparoscopic; f/u: Follow up; IPSS: International Prostatic Symptoms Score.

Table 4 Original studies reporting female urological function

Ref.	Females assessed independently of males	Functional scores applied	Control group	No. of cases examining female urological function	Follow up in months	Outcome summary
Morelli *et al*[30]	Yes	Yes	Robot *vs* lap	Not available	1, 6, 12	No difference between the pre- and post-operative scores in both groups
Luca *et al*[6]	Yes	Yes	No control group	36	1, 6, 12	Worse female urological function at 1 mo with full recovery by 12 mo in both groups
Kim *et al*[31]	No	Yes	Robot *vs* lap	30 rob *vs* 39 lap	1, 3, 6, 12	As in Table 3
Stănciulea *et al*[37]	No	Yes	No control group	78	Once b/n 6 and 12	As in Table 3
Hellan *et al*[34]	No	No	No control group	39	Median f/u 13 mo	As in Table 3
Park *et al*[39]	No	No	No control group	30	Not stated	As in Table 3
Cho *et al*[35]	No	No	Robot *vs* lap	278 *vs* 278	1	As in Table 3

This table describes the same study characteristics included in Table 3 but for female instead of male patients. Robot: Robotic; lap: Laparoscopic; f/u: Follow up.

outcomes (Table 4). However, there are only two studies that report female urological dysfunction independently to that of males.

Both studies used approved functional scores to assess urinary function and both studies compared robotic surgery patients with laparoscopic surgery patients. Morelli *et al*[30] found no difference between the pre-operative and post-operative scores concerning voiding and filling symptoms in both groups. Conversely, Luca *et al*[6] reported worsening of symptoms one month post operatively with full recovery by 12 mo in both robotic and laparoscopic groups.

Male sexual function

Fourteen original studies reported male sexual functional outcomes (Table 5). Ten of those assessed male sexual function *via* the IIEF[42] questionnaire.

Six of the ten studies using the IIEF scores compared the scores of patients receiving robotic rectal cancer surgery with that of a control. Park *et al*[9]'s study showed that sexual function recovers faster in the robotic group. At 6 mo the IIEF scores in the robotic group were higher than in the laparoscopic group and showed a significantly smaller decrease from baseline (P = 0.03). Kim *et al*[31] also found that sexual function recovered quicker in the robotic group (6 mo *vs* 12 mo), but unlike Park *et al*[9]'s study, when comparing the change of total IIEF scores from baseline no significant difference was detected. However, erectile function and libido had deteriorated significantly more in the laparoscopic group 3 mo post op. Park *et al*[32] showed similar results, with significantly higher mean IIEF scores at 3 and 6 mo post op in favour of the robotic group. Like Kim *et al*[31]'s study, the change of scores from baseline did not statistically favour either intervention. In Morelli *et al*[30]'s study erectile and orgasmic function was significantly worse 1 mo after RobTME while it was significantly worse after 1 and 6 mo after LapTME, with erectile and orgasmic function normal at 12 mo in both groups. The other components of the IIEF score deteriorated 1 and 6 mo following surgery in both groups, with normalisation of the scores at 12 mo. D'Annibale *et al*[33] reported better restoration of erectile function 1 year after surgery in the robotic group; however, there is no mention of the actual IIEF scores or their change from baseline in the study so any results need to be interpreted with caution. Overall, the above comparative studies seem to report a trend towards quicker recovery of sexual function in the robotic group. However, Park *et al*[9]'s study was the only one to reveal an interval change in IIEF scores in favour of the robotic group that was statistically significant.

Female sexual function

In contrast to male sexual function, only a few studies have investigated sexual function in females (Table 6). Only three studies have examined female sexual dysfunction independently with that of males[6,30,37] and only one of those compared robotic outcomes to those of a control group[30]. All three studies assessed female sexual function *via* the FSFI.

Morelli *et al*[30] reported worsening of sexual outcomes in both groups 1 and 6 mo following surgery, but sexual outcomes were restored by 12 mo. There were no differences between the robotic and laparoscopic groups. Luca *et al*[6] demonstrated similar results in their robotic group as in Morelli *et al*[30]'s study, whereas Stănciulea *et al*[37] reported no difference between pre- and post-operative FSFI scores.

DISCUSSION

This literature review highlights the fact that the impact of robotic rectal surgery on urogenital functional outcomes is yet to be established. There are number of limitations in the current studies. These include poor study design, small number of participants, lack of stringent follow up and limitations to the methods and types of data collected.

The main limitations of the primary studies were the lack of randomisation, retrospective design and small

Table 5 Original studies reporting male sexual function

Ref.	Males assessed independently of females	Functional scores applied	Control group	No. of cases examining male sexual function	Follow up in months	Outcome summary
Kim *et al*[31]	Yes	Yes	Robot *vs* lap	18 rob *vs* 20 lap	1, 3, 6, 12	Quicker recovery of male sexual function in robotic group (6 mo *vs* 12 mo) No difference in IIEF change from baseline between two groups at any stage Erectile function and libido deteriorated significantly more in lap group at 3 mo
Park *et al*[9]	Yes	Yes	Robot *vs* lap	20 *vs* 20	3, 6, 12	Quicker recovery of male sexual function in robotic group (6 mo *vs* 12 mo) IIEF deterioration significantly higher in lap group at 6 mo (P = 0.03)
Park *et al*[32]	Yes	Yes	Robot *vs* lap	14 rob *vs* 15 lap	3, 6, 12	Better male sexual function scores at 3 and 6 mo in robotic group No difference in IIEF change from baseline between two groups at any stage
D'Annibale *et al*[33]	Yes	Yes	Robot *vs* lap	18 rob *vs* 23 lap	1, 12	Erectile function restored 1 yr post-operatively in robotic group (P = 0.066) and partially in lap group (P = 0.048) No statistical comparison of IIEF change from baseline b/n 2 groups at any stage
Ozeki *et al*[18]	Yes	Yes	Robot *vs* open	15 rob *vs* 22 open	3, 6, 12	IIEF scores unchanged at 3, 6 and 12 mo in both groups
Morelli *et al*[30]	Yes	Yes	Robot *vs* lap	Not available	1, 6, 12	Quicker recovery of erectile and orgasmic function in robotic group (6 mo *vs* 12 mo) No difference in IIEF change from baseline between two groups at any stage
Leung *et al*[5]	Yes	Yes	No control group	15	3	No significant difference between post- and pre-operative IIEF scores
Luca *et al*[6]	Yes	Yes	No control group	38	1, 6, 12	Male sexual function scores decreased at 1 and 6 mo, recovered at 12 mo
Stănciulea *et al*[37]	Yes	Yes	No control group	31	Once b/n 6 and 12	No difference of pre- and post-op IIEF scores with exception of 3 patients (9.68%) with severe erectile dysfunction
Alecu *et al*[36]	No	Yes	No control group	79	Not stated	3 patients (3.79%) developed important sexual dysfunction. No mention of IIEF scores in results
Patriti *et al*[40]	Yes	No	Robot *vs* lap	11 rob *vs* 12 lap	Mean f/u 12 mo	No difference in the incidence of sexual dysfunction between the 2 groups
Erguner *et al*[38]	No	No	Robot *vs* lap	27 rob *vs* 37 lap	Not stated	No difference in the incidence of sexual dysfunction between the 2 groups
Cho *et al*[35]	No	No	Robot *vs* lap	278 *vs* 278	1	No difference in the incidence of sexual dysfunction between the 2 groups
Park *et al*[39]	Yes	No	No control group	16	Not stated	1 patient (6.25%) developed ejaculatory dysfunction, no patients developed erectile dysfunction

This table describes the same study characteristics included in Tables 3 and 4 but for studies assessing male sexual function. Robot: Robotic; lap: Laparoscopic; f/u: Follow up; IIEF: International Index of Erectile Function score.

number of cases in the majority of studies (Tables 1 and 2). As for the prospective studies, most of them failed to mention the number of patients excluded during recruitment, the number of patients refusing to participate and the number of drop outs. There was one RCT but randomisation was abandoned early on as the operating surgeon quickly favoured the robotic approach for low rectal tumours. In terms of participant selection only nine studies reported their outcomes against those of a control, with the other studies essentially only describing their case series rather than comparing them to alternative treatment methods.

Case matching was performed in 2 of the comparative studies[9,35], but in the remaining studies patient selection was susceptible to selection bias due to the method of patient selection and allocation. In a number of studies patients were only able to receive robotic surgery if they covered the extra costs themselves, leaving the patients that couldn't afford it opting for laparoscopic or open surgery instead. Therefore the validity of the data may be skewed since patients that opted for robotic surgery were more likely to be from a higher socio-economic background, which is a potential confounding factor. Moreover, two studies compared their robotic cases with an equivalent number of their first laparoscopic cases[30,33]. This selection method was done to eliminate the confounding factor of a learning curve from either method. However, the learning curve for

Table 6 Original studies reporting female sexual function

Ref.	Females assessed independently of males	Functional scores applied	Control group	No. of cases examining female sexual function	Follow up in months	Outcome summary
Morelli *et al*[30]	Yes	Yes	Robot *vs* lap	not available	1, 6, 12	Female sexual function worse at 1 and 6 mo and restored by 12 mo, in both groups
Luca *et al*[6]	Yes	Yes	No control group	36	1, 6, 12	Female sexual function worse at 1 and 6 mo and restored by 12 mo
Stănciulea *et al*[37]	Yes	Yes	No control group	13	Once b/n 6 and 12	No difference between pre- and post-operative FSFI scores (but data not provided in results section)
Alecu *et al*[36]	No	Yes	No control group	79 pts	Not stated	As in Table 5
Erguner *et al*[38]	No	No	Robot *vs* lap	27 rob *vs* 37 lap	Not stated	As in Table 5
Cho *et al*[35]	No	No	Robot *vs* lap	278 *vs* 278	1	As in Table 5

This table describes the same study characteristics included in Tables 3-5 but for studies assessing female sexual function. Robot: Robotic; lap: Laparoscopic; FSFI: Female Sexual Function Index.

each method is not equal[48] and since in both studies all cases were performed by one surgeon only, it is possible that many of the skills acquired from the laparoscopic method were transferable to the robotic one. This way, results in favour of the robotic group could simply represent advancement in the surgeon's operative technique rather than superiority for the robot.

Patients in the robotic cohort either had a fully robotic procedure or a hybrid procedure (Table 2). The main difference between the two approaches is that in the hybrid approach robotic rectal dissection is preceded by laparoscopic mobilisation of the left colon and ligation of the inferior mesenteric vessels. It is possible that the difference in approach could influence urogenital outcomes. Supporters of the fully robotic approach would advocate that robotic dissection around the inferior mesenteric artery pedicle is an essential step of the procedure for identification and preservation of the periaortic nerves[49], which is where the superior hypogastric plexus lies. Moreover, the paired hypogastric nerves are susceptible to injury during mobilisation of the rectosigmoid colon from the gonadals and the ureter[13]; a step performed laparoscopically during the hybrid approach. Since injury to those nerves can lead to urogenital dysfunction, the hybrid approach might not exploit the full potential of the robotic system.

Five studies did not use functional scores to assess urogenital outcomes. The challenge with only reporting the incidence of urological or sexual dysfunction is not only the inability to quantify the level of dysfunction but also to define what makes a case. Furthermore, where studies fail to report how many of the patients were sexually active pre-operatively, observational bias may be present.

It is important to mention that even though iatrogenic nerve injury is the primary cause of urogenital dysfunction[14-16], this group of symptoms is probably multifactorial in origin. Ozeki *et al*[18] utilised univariate analysis and found that age and post-operative complications significantly affected urinary function and sexual function respectively at 12 mo follow up. Sexual function in comparison to urological function is reported as being influenced by psychological factors and this is the case more so in women[4,6]. Luca *et al*[6] showed that whereas the presence of an ileostomy in men did not influence sexual function, it deeply affected it in women. Furthermore, poor body image, fatigue, depression, loss of independence and changes in relationships have all been identified as important factors in women's sexual dysfunction[4]. In addition, radiation induced ovarian failure in premenopausal women can further worsen sexual symptoms[4]. Since the above are potentially important confounding factors, it is important for the control group to be as similar to the experimental group as possible or control for these confounders in the analysis, something absent in the studies examined in this review.

In this review we did not perform a meta-analysis due to the heterogeneity of the included studies. Nevertheless, it should be mentioned that two review articles have performed meta-analyses on male urological and sexual function scores of patients receiving robotic *vs* laparoscopic rectal surgery[46,47]. For male urological function, the reviews pooled the data from three studies and found that at 3 mo there was a significant difference of IPSS scores in favour of the robotic group. However, this was not the case at 6 mo following surgery and at 12 mo the two meta-analyses reported contradictory results, one showing favourable IPSS scores for the robotic group[46] whilst the other demonstrated no difference between the two groups[47]. Regarding male sexual function, the meta-analyses pooled the data for erectile function only. By including three and two studies respectively[46,47], both reviews demonstrated favourable erectile function scores for the robotic group at 3 and 6 mo following surgery. Weighing these results one should note that as a rule, the overall quality of a meta-analysis is limited to the quality of its primary studies, and since the quality of the evidence available is low, the results of the available meta-analysis are of equally low quality.

There is a degree of inconsistency of results across the research examined in this review and the potential for bias amongst the various studies on the subject. There is a lack of high level evidence supporting any particular approach for preservation of urogenital function following rectal surgery. Nevertheless, the current evidence suggests that robotic surgery might lead to a quicker recovery of male urological and sexual function when compared to alternative methods. It is less clear whether robotic surgery makes any difference in male urogenital outcomes 1 year following surgery. In females the evidence on urogenital function following robotic rectal surgery is further limited. Again functional outcomes seem to improve with time but this is regardless of operative approach.

Larger randomised controlled trials such as the ROLARR trial[50] might provide more insight into this matter. However, even though the ROLARR trial is underway, urogenital outcomes are not one of its primary ends points and urogenital outcomes are only assessed once following surgery, at six months. Therefore, to answer whether robotic rectal cancer surgery truly offers superior urogenital outcomes further randomised control trials specifically designed to evaluate urogenital function with appropriate short and long term follow up are recommended. In addition, urogenital dysfunction should be rigorously assessed through appropriate validated functional scores and males should be analysed separately to females.

COMMENTS

Background

Urological and sexual dysfunctions are unfortunate sequela of rectal cancer surgery. They occur due to iatrogenic injury to the pelvic autonomic nerves during the surgical process and cause significant quality of life limitations for patients. Better visualisation of the pelvis such as during laparoscopy has failed to address this issue due to the stiff, fixed tip instruments used for laparoscopy being hard to use in narrow spaces such as the pelvis. Robotic surgical systems overcome many of the limitations of laparoscopic surgery but whether robotic rectal surgery can lead to superior urological and sexual functional outcomes remains to be determined.

Research frontiers

Robotic surgical systems possess several advantages over conventional laparoscopy such as flexible wristed instruments that mimic the surgeon's hands. They eliminate the surgeon's tremor and offer far superior ergonomics and dexterity. In addition, the surgeon, rather than the assistant, controls a 3-D, high definition stable camera, an important aspect for co-ordinated surgery. These advantages allow for precision surgery in narrow spaces such as the pelvis, where other methods have failed and in rectal surgery could enable preservation of the pelvic autonomic nerves and therefore increase the quality of life for these patients.

Innovations and breakthroughs

There are only a few studies that have investigated the urological and sexual outcomes of robotic rectal surgery and these tend to be predominantly about male patients. This study differs by critically reviewing the available literature on the postoperative urological and sexual outcomes of robotic rectal surgery on both male and female patients. As such, this review is unique in that it examines the largest number or relevant studies to date; it focuses solely on the urogenital outcomes of robotic rectal surgery and examines the evidence on both males and females.

Applications

This review critically analyses the literature examining the urogenital outcomes of robotic rectal cancer surgery. Readers will be able to have a concise understanding of the available literature on this subject. Furthermore, this review leads to clear conclusions indicating a paucity of evidence of whether robotic rectal surgery offers favourable urogenital functional outcomes and establishes quality of life differences. Nevertheless, the authors identify that robotic surgery might lead to a quicker recovery of male urological and sexual function when compared to alternative methods of surgery and recommend the direction of further research.

Terminology

Urogenital function is a term referring to the combination of urological and sexual function. Laparoscopic and robotic surgeries are forms of minimally invasive surgery which offer several advantages over open surgery, such as smaller wounds and quicker postoperative recovery.

Peer-review

The manuscript is a comprehensive review addressing pelvic functions (rectal and sexual) after robotic surgery. Content coverage is adequate and focus. Language quality and flow of idea are excellent.

REFERENCES

1 **Weir HK**, Thun MJ, Hankey BF, Ries LA, Howe HL, Wingo PA, Jemal A, Ward E, Anderson RN, Edwards BK. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst* 2003; **95**: 1276-1299 [PMID: 12953083 DOI: 10.1093/jnci/djg040]

2 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

3 **Siegel R**, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]

4 **Panjari M**, Bell RJ, Burney S, Bell S, McMurrick PJ, Davis SR. Sexual function, incontinence, and wellbeing in women after rectal cancer--a review of the evidence. *J Sex Med* 2012; **9**: 2749-2758 [PMID: 22905761 DOI: 10.1111/j.1743-6109.2012.02894.x]

5 **Leung ALH**, Chan W-H, Cheung HYS, Lui GKL, Fung JTK, Li MKW. Initial experience on the urogenital outcomes after robotic rectal cancer surgery. *Surg Pract* 2013; **17**: 13-17 [DOI: 10.1111/j.1744-1633.2012.00626.x]

6 **Luca F**, Valvo M, Ghezzi TL, Zuccaro M, Cenciarelli S, Trovato C, Sonzogni A, Biffi R. Impact of robotic surgery on sexual and urinary functions after fully robotic nerve-sparing total mesorectal excision for rectal cancer. *Ann Surg* 2013; **257**: 672-678 [PMID: 23001075 DOI: 10.1097/SLA.0b013e318269d03b]

7 **Heald RJ**, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* 1982; **69**: 613-616 [PMID: 6751457 DOI: 10.1007/s11725-008-0110-z]

8 **Heald RJ**, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1**: 1479-1482 [PMID: 2425199 DOI: 10.1016/S0140-6736(86)91510-2]

9 **Park SY**, Choi GS, Park JS, Kim HJ, Ryuk JP, Yun SH. Urinary and erectile function in men after total mesorectal excision by laparoscopic or robot-assisted methods for the treatment of rectal cancer: a case-matched comparison. *World J Surg* 2014; **38**: 1834-1842 [PMID: 24366278 DOI: 10.1007/s00268-013-2419-5]

10 **Kim NK**, Aahn TW, Park JK, Lee KY, Lee WH, Sohn SK, Min JS. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. *Dis Colon Rectum* 2002; **45**: 1178-1185 [PMID: 12352233 DOI: 10.1007/s10350-004-6388-5]

11 **Chang PL**, Fan HA. Urodynamic studies before and/or after abdominoperineal resection of the rectum for carcinoma. *J Urol* 1983; **130**: 948-951 [PMID: 6632107]

12 **Havenga K**, DeRuiter MC, Enker WE, Welvaart K. Anatomical basis of autonomic nerve-preserving total mesorectal excision for rectal cancer. *Br J Surg* 1996; **83**: 384-388 [PMID: 8665201 DOI: 10.1002/bjs.1800830329]

13 **Kim NK**, Kim YW, Cho MS. Total mesorectal excision for rectal cancer with emphasis on pelvic autonomic nerve preservation: Expert technical tips for robotic surgery. *Surg Oncol* 2015; **24**: 172-180 [PMID: 26141555 DOI: 10.1016/j.suronc.2015.06.012]

14 **Lange MM**, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. *Nat Rev Urol* 2011; **8**: 51-57 [PMID: 21135876 DOI: 10.1038/nrurol.2010.206]

15 **Havenga K**, Enker WE. Autonomic nerve preserving total mesorectal excision. *Surg Clin North Am* 2002; **82**: 1009-1018 [PMID: 12507206 DOI: 10.1016/S0039-6109(02)00044-0]

16 **Masui H**, Ike H, Yamaguchi S, Oki S, Shimada H. Male sexual function after autonomic nerve-preserving operation for rectal cancer. *Dis Colon Rectum* 1996; **39**: 1140-1145 [PMID: 8831531 DOI: 10.1007/BF02081416]

17 **Lindsey I**, Guy RJ, Warren BF, Mortensen NJ. Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon. *Br J Surg* 2000; **87**: 1288-1299 [PMID: 11044153 DOI: 10.1046/j.1365-2168.2000.01542.x]

18 **Ozeki S**, Maeda K, Hanai T, Masumori K, Katsuno H, Takahashi H. Effects of robotic rectal surgery on sexual and urinary functions in male patients. *Surg Today* 2016; **46**: 491-500 [PMID: 26198896 DOI: 10.1007/s00595-015-1217-0]

19 **Lim RS**, Yang TX, Chua TC. Postoperative bladder and sexual function in patients undergoing surgery for rectal cancer: a systematic review and meta-analysis of laparoscopic versus open resection of rectal cancer. *Tech Coloproctol* 2014; **18**: 993-1002 [PMID: 25056719 DOI: 10.1007/s10151-014-1189-x]

20 **McGlone ER**, Khan O, Flashman K, Khan J, Parvaiz A. Urogenital function following laparoscopic and open rectal cancer resection: a comparative study. *Surg Endosc* 2012; **26**: 2559-2565 [PMID: 22476834 DOI: 10.1007/s00464-012-2232-5]

21 **Jones OM**, Stevenson AR, Stitz RW, Lumley JW. Preservation of sexual and bladder function after laparoscopic rectal surgery. *Colorectal Dis* 2009; **11**: 489-495 [PMID: 18637928 DOI: 10.1111/j.1463-1318.2008.01642.x]

22 **Katsios CG**, Baltogiannis G. Laparoscopic sphincter-preserving rectal cancer surgery: a highly demanding procedure. *Surg Endosc* 2010; **24**: 3241-3243 [PMID: 20372934 DOI: 10.1007/s00464-010-1025-y]

23 **Schwab KE**, Dowson HM, Van Dellen J, Marks CG, Rockall TA. The uptake of laparoscopic colorectal surgery in Great Britain and Ireland: a questionnaire survey of consultant members of the ACPGBI. *Colorectal Dis* 2009; **11**: 318-322 [PMID: 18573117 DOI: 10.1111/j.1463-1318.2008.01601.x]

24 **Guillou PJ**, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 1718-1726 [PMID: 15894098 DOI: 10.1016/S0140-6736(05)66545-2]

25 **van der Pas MH**, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013; **14**: 210-218 [PMID: 23395398 DOI: 10.1016/S1470-2045(13)70016-0]

26 **deSouza AL**, Prasad LM, Marecik SJ, Blumetti J, Park JJ, Zimmern A, Abcarian H. Total mesorectal excision for rectal cancer: the potential advantage of robotic assistance. *Dis Colon Rectum* 2010; **53**: 1611-1617 [PMID: 21178854 DOI: 10.1007/DCR.0b013e3181f22f1f]

27 **Park JS**, Choi GS, Lim KH, Jang YS, Jun SH. S052: a comparison of robot-assisted, laparoscopic, and open surgery in the treatment of rectal cancer. *Surg Endosc* 2011; **25**: 240-248 [PMID: 20552367 DOI: 10.1007/s00464-010-1166-z]

28 **Fernandez R**, Anaya DA, Li LT, Orcutt ST, Balentine CJ, Awad SA, Berger DH, Albo DA, Artinyan A. Laparoscopic versus robotic rectal resection for rectal cancer in a veteran population. *Am J Surg* 2013; **206**: 509-517 [PMID: 23809672 DOI: 10.1016/j.amjsurg.2013.01.036]

29 **Xiong B**, Ma L, Zhang C, Cheng Y. Robotic versus laparoscopic total mesorectal excision for rectal cancer: a meta-analysis. *J Surg Res* 2014; **188**: 404-414 [PMID: 24565506 DOI: 10.1016/j.jss.2014.01.027]

30 **Morelli L**, Ceccarelli C, Di Franco G, Guadagni S, Palmeri M, Caprili G, D'Isidoro C, Marciano E, Pollina L, Campani D, Massimetti G, Di Candio G, Mosca F. Sexual and urinary functions after robot-assisted versus pure laparoscopic total mesorectal excision for rectal cancer. *Int J Colorectal Dis* 2016; **31**: 913-915 [PMID: 26149941 DOI: 10.1007/s00384-015-2301-z]

31 **Kim JY**, Kim NK, Lee KY, Hur H, Min BS, Kim JH. A comparative study of voiding and sexual function after total mesorectal excision with autonomic nerve preservation for rectal cancer: laparoscopic versus robotic surgery. *Ann Surg Oncol* 2012; **19**: 2485-2493 [PMID: 22434245 DOI: 10.1245/s10434-012-2262-1]

32 **Park SY**, Choi GS, Park JS, Kim HJ, Ryuk JP. Short-term clinical outcome of robot-assisted intersphincteric resection for low rectal cancer: a retrospective comparison with conventional laparoscopy. *Surg Endosc* 2013; **27**: 48-55 [PMID: 22752275 DOI: 10.1007/s00464-012-2405-2]

33 **D'Annibale A**, Pernazza G, Monsellato I, Pende V, Lucandri G, Mazzocchi P, Alfano G. Total mesorectal excision: a comparison of oncological and functional outcomes between robotic and laparoscopic surgery for rectal cancer. *Surg Endosc* 2013; **27**: 1887-1895 [PMID: 23292566 DOI: 10.1007/s00464-012-2731-4]

34 **Hellan M**, Anderson C, Ellenhorn JD, Paz B, Pigazzi A. Short-term outcomes after robotic-assisted total mesorectal excision for rectal cancer. *Ann Surg Oncol* 2007; **14**: 3168-3173 [PMID: 17763911 DOI: 10.1245/s10434-007-9544-z]

35 **Cho MS**, Baek SJ, Hur H, Min BS, Baik SH, Lee KY, Kim NK. Short and long-term outcomes of robotic versus laparoscopic total mesorectal excision for rectal cancer: a case-matched retrospective study. *Medicine* (Baltimore) 2015; **94**: e522 [PMID: 25789947 DOI: 10.1097/MD.0000000000000522]

36 **Alecu L**, Stănciulea O, Poesina D, Tomulescu V, Vasilescu C, Popescu I. Robotically performed total mesorectal excision for rectal cancer. *Chirurgia* (Bucur) 2015; **110**: 137-143 [PMID: 26011835]

37 **Stănciulea O**, Eftimie M, David L, Tomulescu V, Vasilescu C, Popescu I. Robotic surgery for rectal cancer: a single center experience of 100 consecutive cases. *Chirurgia* (Bucur) 2013; **108**: 143-151 [PMID: 23618561]

38 **Erguner I**, Aytac E, Boler DE, Atalar B, Baca B, Karahasanoglu T, Hamzaoglu I, Uras C. What have we gained by performing robotic rectal resection? Evaluation of 64 consecutive patients who underwent laparoscopic or robotic low anterior resection for rectal adenocarcinoma. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 316-319 [PMID: 23752000 DOI: 10.1097/SLE.0b013e31828e3697]

39 **Park IJ**, You YN, Schlette E, Nguyen S, Skibber JM, Rodriguez-Bigas MA, Chang GJ. Reverse-hybrid robotic mesorectal excision for rectal cancer. *Dis Colon Rectum* 2012; **55**: 228-233 [PMID: 22228169 DOI: 10.1097/DCR.0b013e31823c0bd2]

40 **Patriti A**, Ceccarelli G, Bartoli A, Spaziani A, Biancafarina A, Casciola L. Short- and medium-term outcome of robot-assisted and traditional laparoscopic rectal resection. *JSLS* 2009; **13**: 176-183 [PMID: 19660212]

41 **Park YW**, Lee JH. Correlation between the visual prostate symptom score and international prostate symptom score in patients with lower urinary tract symptoms. *Int Neurourol J* 2014; **18**: 37-41 [PMID: 24729926 DOI: 10.5213/inj.2014.18.1.37]

42 **Rosen RC**, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822-830 [PMID: 9187685 DOI: 10.1016/S0090-4295(97)00238-0]

43 **Rosen R**, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment

of female sexual function. *J Sex Marital Ther* 2000; **26**: 191-208 [PMID: 10782451 DOI: 10.1080/009262300278597]

44 **Donovan JL**, Peters TJ, Abrams P, Brookes ST, de aa Rosette JJ, Schäfer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. *J Urol* 2000; **164**: 1948-1955 [PMID: 11061889 DOI: 10.1016/S0022-5347(05)66926-1]

45 **Brookes ST**, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. *Am J Obstet Gynecol* 2004; **191**: 73-82 [PMID: 15295345 DOI: 10.1016/j.ajog.2003.12.027]

46 **Broholm M**, Pommergaard HC, Gögenür I. Possible benefits of robot-assisted rectal cancer surgery regarding urological and sexual dysfunction: a systematic review and meta-analysis. *Colorectal Dis* 2015; **17**: 375-381 [PMID: 25515638 DOI: 10.1111/codi.12872]

47 **Lee SH**, Lim S, Kim JH, Lee KY. Robotic versus conventional laparoscopic surgery for rectal cancer: systematic review and meta-analysis. *Ann Surg Treat Res* 2015; **89**: 190-201 [PMID: 26448918 DOI: 10.4174/astr.2015.89.4.190]

48 **Pai A**, Melich G, Marecik SJ, Park JJ, Prasad LM. Current status of robotic surgery for rectal cancer: A bird's eye view. *J Minim Access Surg* 2015; **11**: 29-34 [PMID: 25598596 DOI: 10.4103/0972-9941.147682]

49 **Aly EH**. Robotic colorectal surgery: summary of the current evidence. *Int J Colorectal Dis* 2014; **29**: 1-8 [PMID: 23995270 DOI: 10.1007/s00384-013-1764-z]

50 **Collinson FJ**, Jayne DG, Pigazzi A, Tsang C, Barrie JM, Edlin R, Garbett C, Guillou P, Holloway I, Howard H, Marshall H, McCabe C, Pavitt S, Quirke P, Rivers CS, Brown JM. An international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. *Int J Colorectal Dis* 2012; **27**: 233-241 [PMID: 21912876 DOI: 10.1007/s00384-011-1313-6]

51 **Scarpinata R**, Aly EH. Does robotic rectal cancer surgery offer improved early postoperative outcomes? *Dis Colon Rectum* 2013; **56**: 253-262 [PMID: 23303155 DOI: 10.1097/DCR.0b013e3182694595]

52 **Pigazzi A**, Ellenhorn JD, Ballantyne GH, Paz IB. Robotic-assisted laparoscopic low anterior resection with total mesorectal excision for rectal cancer. *Surg Endosc* 2006; **20**: 1521-1525 [PMID: 16897284 DOI: 10.1007/s00464-005-0855-5]

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CASE REPORT

Gallstone ileus associated with impaction at Meckel's diverticulum: Case report and literature review

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Author contributions: Lamba HK and Prabhu A performed the surgery, and managed post-operative care of patient; Prabhu A collected the patient's clinical data; Lamba HK and Shi Y designed the case report, analyzed the clinical data and wrote the paper.

Institutional review board statement: The study was reviewed and approved by the University Hospitals Case Medical Center Institutional Review Board.

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Abstract

Gallstone ileus due to erosion of one or more gallstones into the gastrointestinal tract is an uncommon cause of small bowel obstruction. The site of impaction is usually distal ileum, and less commonly the jejunum, colon, duodenum, or stomach. We report a rare case of gallstone ileus with impaction at the proximal small bowel and at a Meckel's diverticulum (MD) in a 64-year-old woman managed with laparoscopic converted to open small bowel resections. Patient was discharged home in stable condition and remained asymptomatic at 6-mo follow up. We review the current literature on surgical approaches to MD and gallstone ileus. Diverticulectomy or segmental resection is preferred for complicated MD. For gallstone ileus, simple enterolithotomy or segmental resection are the most the most favored especially in older co-morbid patients due to lower mortality rates and the rarity of recurrent gallstone ileus. In addition, laparoscopy has been increasingly reported as a safe approach to manage gallstone ileus.

Key words: Gallstone ileus; Meckel's diverticulum; Small bowel obstruction; Laparoscopy; Cholecystoenteric fistula; Laparoscopy

Core tip: Gallstone ileus is an uncommon cause of small bowel obstruction in the population at large but is responsible for up to a quarter of mechanical bowel obstructions in the elderly in the United States. We report a rare case of gallstone ileus with impaction at the jejunum and at a Meckel's diverticulum in a 64-year-old female managed by laparoscopic converted to

open segmental bowel resections. We review current literature comparing surgical procedures for Meckel's diverticulum and gallstone ileus.

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INTRODUCTION

We are reporting a case of gallstone ileus involving multiple gallstones managed by laparoscopic converted to open small bowel resections of impacted stones at the jejunum and at a Meckel's diverticulum (MD). MD is the most common congenital anomaly of the gastrointestinal tract and is caused by the incomplete obliteration of the omphalomesenteric duct[1]. It can be found in nearly 2 percent of the population but in most cases it remains asymptomatic[2]. Most reported complications include bleeding, infection and obstruction[3]. Gallstone ileus is an uncommon cause of obstructions in the general population but is responsible for 25% of mechanical bowel obstructions in the elderly[4-6]. We found only 3 other case reports with mention of gallstone impaction at MD[7-9].

CASE REPORT

A 64-year-old morbidly obese woman with a history of diabetes, hypertension, and atrial fibrillation presented to an outside hospital (OSH) for PO intolerance with nausea, bilious emesis, and post-prandial abdominal pain. Computerized tomography (CT) of abdomen and pelvis demonstrated small bowel obstruction. Hepatobiliary iminodiacetic acid scan was performed and demonstrated probable mass in the second portion of the duodenum. She was transferred to our institution for escalation of care where she was found to be tachypneic, tachycardic and in atrial fibrillation. On abdominal exam she was distended and mildly tender without rebound or guarding. Her white blood cell count was 14.9 without left shift. She was admitted to the medical intensive care unit for respiratory failure and metabolic acidosis in the setting of frequent bilious emesis.

Repeat CT of the abdomen and pelvis at our institution demonstrated pneumobilia, small bowel dilation and intraluminal small bowel filling defects consistent with cholecystoduodenal fistula with gallstone ileus. Three gallstones were identified, one in the jejunum and two in the ileum along with a mechanical small bowel obstruction with a transition point near the distal calculi in the distal jejunum/proximal ileum (Figure 1). She was taken to the operating room for laparoscopic small bowel resection.

During laparoscopy, bleeding from the deep inferior epigastric vessels necessitated conversion to laparotomy. The small bowel was then run and a large gallstone was found to be obstructing the distal jejunum. We also identified a MD impacted with two smaller stones. A longitudinal incision was made in the jejunum to remove the stone and perform an enterolithotomy. However due to significant edema and inability to milk the stone distally, a small bowel resection was performed.

Once this was complete, we turned our attention to the MD and performed a small bowel resection to include the MD with approximately 5 cm of adjacent small bowel. This resection was performed in lieu of a diverticulectomy due to concern about narrowing of the small bowel lumen. At the end of the surgery the patient required pressor support. She was kept intubated and transferred to the surgical intensive care unit.

Patient recovered bowel function on postoperative day 4 but her postoperative course was remarkable for a midline incision hematoma secondary to treatment with therapeutic Lovenox for previous history of atrial fibrillation. She required wound opening, evacuation, and packing. Patient subsequently remained stable on Lovenox without further bleeding episodes and was eventually discharged in stable condition to a skilled nursing facility. Upon follow up, 6 mo later, patient was asymptomatic.

Pathological examination of the surgical specimen demonstrated mucosal ulceration and transmural inflammation of both of the resected bowel segments. The stone found in the jejunum was identified as a mixed type gallstone measuring 4.7 cm × 3.2 cm × 3.2 cm and the stones found at the MD were identified as mixed type gallstones measuring 4.0 cm× 2.7 cm × 2.7 cm and 2.5 cm × 2.0 cm × 1.4 cm (Figure 2).

DISCUSSION

Gallstone ileus is an uncommon complication, occurring in 0.3% to 0.5% of all cases of cholelithiasis, and accounting for 1% to 4% of mechanical small bowel obstructions. However, while gallstone ileus is rare in the general population, it accounts for 25% of mechanical bowel obstructions in patients over 65 years of age in the United States[4-6]. Because of the advanced age at presentation, patients often have multiple comorbidities, which contribute to the high morbidity and mortality associated with gallstone ileus. The pathophysiology of gallstone ileus involves the erosion of one or more gallstones from a chronically inflamed gallbladder into the gastrointestinal tract, creating a cholecystenteric fistula. Gallstones less than 2 to 2.5 cm generally pass into the intestine without causing obstruction while stones 5 cm or larger are more likely to impact usually at the distal ileum, the narrowest part of the small bowel[10]. Other reported sites of impaction include proximal ileum, jejunum, colon, and rarely the duodenum or stomach (Bouveret's syndrome)[11]. In our case, a large,

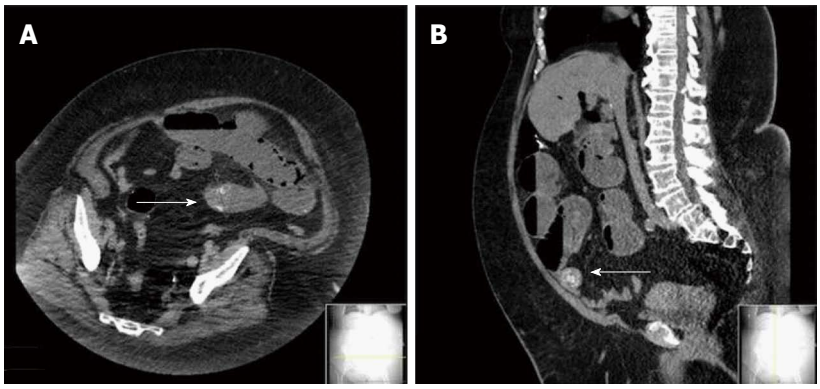

Figure 1 Computed tomography of abdomen pelvis without contrast. A: Axial section demonstrating 31.8 mm gallstone (arrow) in jejumum; B: Sagital section demonstrating transition point and smaller gallstone (arrow) at proximal ileum.

Figure 2 Gross specimen of Meckel's diverticulum impacted with two gallstones.

approximately 5 cm, gallstone was found impacted at the jejunum while two smaller stones were found impacted at a MD. Clinical presentation of gallstone ileus is variable and often insidious. Patients can have painless intervals due to "tumbling" or incomplete small bowel obstruction in which the impacted stone intermittently passes and lodges in the intestinal lumen, until the stone either passes through the gastrointestinal tract or is impacted. It is possible this pattern of remitting symptoms may have contributed to the delay in diagnosis for our patient after her initial presentation to the OSH.

MD is a common congenital anomaly of the small intestine occurring in up to 3% of the population, typically 55 cm from the ileocecal valve[8]. It is usually asymptomatic, with a low lifetime risk of developing complications, with most occurring later in adulthood. Most reported complications include obstruction, hemorrhage, perforation, and neoplasia[8]. Small bowel obstruction can be caused by intessusception or volvulus of MD. In rare cases enteroliths, can form within a MD and cause an obstruction from impaction within the small bowel. Stasis in the diverticulum in combination with the alkalotic environment of the small bowel can promote precipitation of calcium and is thought to contribute to formation of an MD enterolith[7]. In our case the patient had an impaction of a gallstone in the MD. This is exceptionally rare with only 3 cases having been reported in the literature.

Impaction of a gallstone at MD can cause intermittent abdominal pain, bleeding, diverticulitis, perforation or small bowel obstruction (SBO). The presence of stones in a MD predispose to SBO by promoting local inflammation of the diverticulum and intussusception or by impaction of the stone in the bowel following its extrusion from the diverticulum. Clinical differentiation of MD enterolith from gallstone ileus can be difficult as both present similarly with bowel obstruction with prolonged indolent course. Pneumobilia on abdominal plain film suggests gallstone ileus but abdominal film has very low sensitivity for detecting gallstone ileus or MD enterolith[12]. CT is the ideal diagnostic modality with sensitivity, specificity and diagnostic accuracy of over 93%[13]. However, gallstone ileus is often diagnosed only at the time of laparotomy in up to 25% to 50% of cases[5,14,15].

The surgical management of an incidentally found MD in the adult population remains controversial. Most surgeons would advise removing an asymptomatic diverticulum when found incidentally at laparotomy in pediatric patients and young adults secondary to the seemingly significant risk of developing complications. However, the literature is less decisive regarding prophylactic resection in adults. For example, Peoples *et al*[16] found a high morbidity and mortality rate associated with resection but low lifetime risk (6.2%) of developing symptoms from a MD, with the majority of complications occurring during the first 2 decades of life. Cullen *et al*[17] demonstrated operative morbidity and mortality for elective MD resection (2% and 1%) was significantly lower as compared to non-elective resection (12% and 2%)[17]. However, Zani *et al*[18] pointed out 758 resections would have to be performed to prevent one death when consideration is given to the overall low number of patients affected by MD. Therefore, incidental diverticulectomy is generally discouraged, with exception in cases of narrow base,

long length, and palpable heterotopic tissue, where operative management is given special consideration.

On the other hand, it is more uniformly accepted that complicated and symptomatic MD requires operative management. The operative management options for MD with gallstone impaction include gallstone fragmentation and milking into the proximal colon, or gallstone removal thought an enterotomy. The diverticulum itself should also be resected to prevent recurrent stone formation and further complications. The decision to perform a diverticulectomy or segmental resection remains contested. The diverticulum can be easily resected with a stapler without entering the bowel's lumen[19]. However, bowel resection with primary anastomosis is indicated in cases of inflammation, perforation, and necrotic bowel. As in our case, if the small bowel lumen is in danger of being narrowed or the neck of the diverticulum is wide, a segmental resection is favored over a simple diverticulectomy[8]. As far as we know, there are no studies directly comparing diverticulectomy with segmental resection.

The operative management of gallstone impaction of the small bowel are: (1) enterolithotomy, cholecystectomy and fistula repair (single-stage surgery); (2) enterolithotomy with delayed cholecystectomy and fistula closure (two-stage surgery) and (3) simple enterolithotomy (most reported surgical procedure). Proponents of the single-stage procedure cite recurrence and increased risk of developing cholangitis or gallbladder carcinoma as reasons for performing concurrent cholecystectomy and fistula closure[20]. Those who support the two-stage procedure or simple enterolithotomy point to high mortality rates of single-stage procedures and low rates of recurrence and gallbladder carcinoma as reasons for deferring cholecystectomy or avoiding it altogether. Furthermore, fistulas have been shown to close spontaneously once the distal obstruction is removed[20].

No randomized trial has been performed to address the question of appropriate treatment due to the ethical implausibility of randomizing patients to one group over the other. The literature on gallstone ileus is largely limited to retrospective studies or case series (Table 1). In one of the largest studies comparing outcomes between single stage and simple enterolithotomy, Reisner *et al*[5] reviewed 1001 cases and found that a single-stage procedure had a higher mortality rate at 16.9% compared to 11.7% with simple enterolithotomy ($P < 0.17$). Moreover, recurrence rates, from retained stones missed during initial surgery or formation of new gallstones, were the same in both groups.

Thus, the one-stage procedure, while associated with higher mortality rates, did not reduce recurrence rates as its proponents have predicted. Confirming these findings is a review by Halabi *et al*[21] which now exceeds Reisner and Cohen as the largest review of gallstone ileus. They used the Nationwide Inpatient Sample from 2004 to 2009 to compare data for 3268 patients. They found fistula repair and bowel resection to be independently associated with higher mortality rates and longer hospital stays when compared to simple enterolithotomy repair with an odds ratio of 2.86 (95%CI: 1.16-7.07) and 3.68 (95%CI: 1.59-5.76), respectively. In support of these studies are reviews by several other authors showing a preference for reserving the higher risk single-stage procedure for patients with lower ASA classifications[14,22,23].

Table 1 Mortality rates of two main surgical approaches in treating gallstone ileus, one-stage and two-stage procedure

Ref.	With cholecystectomy (single-stage)		Without cholecystectomy (two-stage)		Total
	Total	Mortality	Total	Mortality	
Kasahara *et al*[15]	105	19%	7	0%	112
Reisner *et al*[5]	113	16.8%	801	11.7%	1001
Doko *et al*[36]	19	10.5%	11	9.1%	30
Tan *et al*[37]	12	0%	7	0%	19
Mallipeddi *et al*[23]	14	7.1%	113	5.3%	127
Halabi *et al*[21]	741	7.3%	2527	6.5%	3268

Just as with initial presentation, management options for recurrent gallstone ileus include simple enterolithotomy, single-stage, and two-stage surgery. In a systematic literature review, Mir *et al*[24] compared treatment options in patients with recurrent gallstone ileus over the last 25 years and found a significantly lower mortality rate of simple enterolithotomy when compared to single-stage surgery (4.8% *vs* 22.2%). Several case reports of recurrent gallstone ileus successfully managed by repeat enterolithotomies lend support to this approach[25-27].

A new development in the surgical management of gallstone ileus is the use of laparoscopy. There is to date one retrospective review of laparoscopic assisted *vs* open enterolithotomy of gallstone ileus by Moberg *et al*[28]. Both groups had a similar duration of operation (60 min *vs* 58 min), similar median hospital stay (10 d *vs* 7 d), and similar complication rates (6 *vs* 5), and no deaths. In support of this is the publication of several recent case reports demonstrating the successful use of laparoscopic assisted surgery for gallstone management[29-31]. Moreover, many case reports have been published on the efficacy of a totally laparoscopic approach in the management of gallstone ileus[32-37]. However, in these reports only a single stone was involved. Our attempt at laparoscopic enterolithotomy was limited by bleeding from injury to the epigastric artery during port insertion and was complicated by involvement of multiple stones.

While mortality rates remain high for patients with gallstone ileus they are overall lower in more recent literature, which is likely a reflection of improved modern surgical and peri-operative care. A laparoscopic approach may be suited for the uncomplicated patient with a single stone who can tolerate the longer operative time required to close the enterolithotomy. However, com-

plicated cases such as impaction at a Meckel's diverticulum in a morbidly obese high-risk patient will benefit from an open approach. In such patients, diverticulectomy or segmental bowel resection of the should be strongly considered. These patients then have the option of undergoing an elective cholecystectomy at a later time. Patients who develop recurrence can be managed similarly. A single-stage procedure is rarely performed, typically in lower risk patients, or those with conditions requiring urgent attention to the gallbladder. It is associated with high mortality and morbidity and the decision to perform a single-stage procedure should be weighed carefully against the perceived benefits.

COMMENTS

Case characteristics

A 64-year-old female morbidly obese female with a history of diabetes, hypertension, an atrial fibrillation presented with post-parandial abdominal pain and bilious emesis.

Clinical diagnosis

Gallstone ileus with impaction in small bowel and at Meckel's diverticulum (MD).

Differential diagnosis

The differential diagnosis in this patient involves other causes of small bowel obstruction and mesenteric ischemia, which includes.

Laboratory diagnosis

Leukocytosis with left shift and metabolic acidosis were found in setting of frequent bilious emesis.

Imaging diagnosis

Hepatobiliary iminodiacetic acid scan demonstrating probable mass in small bowel and CT of abdomen and pelvis demonstrating pneumobilia, small bowl dilation and intraluminal small bowel filling defects were consistent with gallstone ileus.

Pathological diagnosis

Surgical small bowel specimen demonstrated distal jejunum with 4.7 cm stone and MD with two gallstones measuring 4 and 2.7 cm.

Treatment

Operative management with laparotomy, enter lithotomy of impacted jejunum, and small bowel resection of impacted MD.

Related reports

Other case reports of gallstone ileus associated with impacted MD have been very rarely presented in the literature. To our knowledge only three cases (two in English and one in Danish) have been published with varying presentations and varying treatment modalities.

Experiences and lessons

Gallstone ileus, while a rare occurrence over all is a more common cause of small bowel obstruction in the elderly and carries a high rate of morbidity and mortality making early clinical suspicion and intervention very important.

Peer-review

This is an important presentation of a rare finding that explores the appropriate management of gallstone ileus in an elderly co-morbid patient with an incidental finding of MD. It is accompanied by a very thorough and well written literature review of management of both symptomatic Meckel's diverticulum and gallstone.

REFERENCES

1 **Cullen JJ**, Kelly KA. Current management of Meckel's diverticulum. *Adv Surg* 1996; **29**: 207-214 [PMID: 8720004]
2 **Moore TC**. Omphalomesenteric duct malformations. *Semin Pediatr Surg* 1996; **5**: 116-123 [PMID: 9138710]
3 **Sharma RK**, Jain VK. Emergency surgery for Meckel's diverticulum. *World J Emerg Surg* 2008; **3**: 27 [PMID: 18700974 DOI: 10.1186/1749-7922-3-27]
4 **Day EA**, Marks C. Gallstone ileus. Review of the literature and presentation of thirty-four new cases. *Am J Surg* 1975; **129**: 552-558 [PMID: 1130595 DOI: 10.1016/0002-9610(75)90315-3]
5 **Reisner RM**, Cohen JR. Gallstone ileus: a review of 1001 reported cases. *Am Surg* 1994; **60**: 441-446 [PMID: 8198337]
6 **Park P**, Mallat AF. Cholecystoduodenal Fistula In JB Dimick, GR Upchurch, CJ Sonnenday. Clinical Scenarios in Surgery: Decision Making and Operative Technique. Philadelphia, PA: Lippincott Williams & Wilkins, 2012: 166 [DOI: 10.1097/SLA.0000000000000353]
7 **Nakamoto Y**, Saga T, Fujishiro S, Washida M, Churiki M, Matsuda K. Gallstone ileus with impaction at the neck of a Meckel's diverticulum. *Br J Radiol* 1998; **71**: 1320-1322 [PMID: 10319010]
8 **Simonsen L**, Schrøder M. Simultaneous occurrence of a stone in an inflamed Meckel's diverticulum and gallstone ileus. *Ugeskr Laeger* 1987; **149**: 601-602 [PMID: 3824672]
9 **Maclean W**, Szentpáli K. Large gallstone impaction at a Meckel's diverticulum causing perforation and localized peritonitis: report of a case. *J Surg Case Rep* 2013; **2013**: pii: rjt097 [PMID: 24968430 DOI: 10.1093/jscr/rjt097]
10 **Beuran M**, Ivanov I, Venter MD. Gallstone ileus--clinical and therapeutic aspects. *J Med Life* 2010; **3**: 365-371 [PMID: 21254732]
11 **Abou-Saif A**, Al-Kawas FH. Complications of gallstone disease: Mirizzi syndrome, cholecystocholedochal fistula, and gallstone ileus. *Am J Gastroenterology* 2002; **97**: 249–254 [DOI: 10.1111/j.1572-0241.2002.05863.x]
12 **Ripollés T**, Miguel-Dasit A, Errando J, Morote V, Gómez-Abril SA, Richart J. Gallstone ileus: increased diagnostic sensitivity by combining plain film and ultrasound. *Abdom Imaging* 2001; **26**: 401-405 [PMID: 11441553 DOI: 10.1007/s002610000190]
13 **Yu CY**, Lin CC, Shyu RY, Hsieh CB, Wu HS, Tyan YS, Hwang JI, Liou CH, Chang WC, Chen CY. Value of CT in the diagnosis and management of gallstone ileus. *World J Gastroenterol* 2005; **11**: 2142-2147 [PMID: 15810081 DOI: 10.3748/wjg.v11.i14.2142]
14 **Clavien PA**, Richon J, Burgan S, Rohner A. Gallstone ileus. *Br J Surg* 1990; **77**: 737-742 [PMID: 2200556 DOI: 10.1002/bjs.1800770707]
15 **Kasahara Y**, Umemura H, Shiraha S, Kuyama T, Sakata K, Kubota H. Gallstone ileus. Review of 112 patients in the Japanese literature. *Am J Surg* 1980; **140**: 437-440 [PMID: 7425220 DOI: 10.1016/0002-9610(80)90185-3]
16 **Peoples JB**, Lichtenberger EJ, Dunn MM. Incidental Meckel's diverticulectomy in adults. *Surgery* 1995; **118**: 649-652 [PMID: 7570318 DOI: 10.1016/S0039-6060(05)80031-5]
17 **Cullen JJ**, Kelly KA, Moir CR, Hodge DO, Zinsmeister AR, Melton LJ. Surgical management of Meckel's diverticulum. An epidemiologic, population-based study. *Ann Surg* 1994; **220**: 564-568; discussion 568-569 [PMID: 7944666 DOI: 10.1097/00000658-199410000-00014]
18 **Zani A**, Eaton S, Rees CM, Pierro A. Incidentally detected Meckel diverticulum: to resect or not to resect? *Ann Surg* 2008; **247**: 276-281 [PMID: 18216533 DOI: 10.1097/SLA.0b013e31815aaaf8]
19 **Matsagas MI**, Fatouros M, Koulouras B, Giannoukas AD. Incidence, complications, and management of Meckel's diverticulum. *Arch Surg* 1995; **130**: 143-146 [PMID: 7848082 DOI: 10.2214/AJR.06.1257]
20 **Berliner SD**, Burson LC. One-stage repair for cholecyst-duodenal fistula and gallstone ileus. *Arch Surg* 1965; **90**: 313-316 [PMID: 14232966 DOI: 10.1001/archsurg.1965.01320080137028]
21 **Halabi WJ**, Kang CY, Ketana N, Lafaro KJ, Nguyen VQ, Stamos MJ, Imagawa DK, Demirjian AN. Surgery for gallstone ileus: a nationwide comparison of trends and outcomes. *Ann Surg* 2014; **259**: 329-335 [PMID: 23295322 DOI: 10.1097/SLA.0b013e31827eefed]

22 **Pavlidis TE**, Atmatzidis KS, Papaziogas BT, Papaziogas TB. Management of gallstone ileus. *J Hepatobiliary Pancreat Surg* 2003; **10**: 299-302 [PMID: 14598150 DOI: 10.1007/s00534-002-0806-7]

23 **Mallipeddi MK**, Pappas TN, Shapiro ML, Scarborough JE. Gallstone ileus: revisiting surgical outcomes using National Surgical Quality Improvement Program data. *J Surg Res* 2013; **184**: 84-88 [PMID: 23764312 DOI: 10.1016/j.jss.2013.05.027]

24 **Mir SA**, Hussain Z, Davey CA, Miller GV, Chintapatla S. Management and outcome of recurrent gallstone ileus: A systematic review. *World J Gastrointest Surg* 2015; **7**: 152-159 [PMID: 26328035 DOI: 10.4240/wjgs.v7.i8.152]

25 **Doogue MP**, Choong CK, Frizelle FA. Recurrent gallstone ileus: underestimated. *Aust N Z J Surg* 1998; **68**: 755-756 [PMID: 9814734]

26 **Webb LH**, Ott MM, Gunter OL. Once bitten, twice incised: recurrent gallstone ileus. *Am J Surg* 2010; **200**: e72-e74 [PMID: 20851377 DOI: 10.3121/cmr.2012.1079]

27 **Pronio A**, Piroli S, Caporilli D, Ciamberlano B, Coluzzi M, Castellucci G, Vestri A, Pitasi F, Montesani C. Recurrent gallstone ileus: case report and literature review. *G Chir* 2013; **34**: 35-37 [PMID: 23463931]

28 **Moberg AC**, Montgomery A. Laparoscopically assisted or open enterolithotomy for gallstone ileus. *Br J Surg* 2007; **94**: 53-57 [PMID: 17058318 DOI: 10.1002/bjs.5537]

29 **Sarli L**, Pietra N, Costi R, Gobbi S. Gallstone ileus: laparoscopic-assisted enterolithotomy. *J Am Coll Surg* 1998; **186**: 370-371 [PMID: 9510270 DOI: 10.1016/S1072-7515(97)00151-8]

30 **Soto DJ**, Evan SJ, Kavic MS. Laparoscopic management of gallstone ileus. *JSLS* 2001; **5**: 279-285 [PMID: 11548836]

31 **Montgomery A**. Laparoscope-guided enterolithotomy for gallstone ileus. *Surg Laparosc Endosc* 1993; **3**: 310-314 [PMID: 8269250]

32 **Zygomalas A**, Karamanakos S, Kehagias I. Totally laparoscopic management of gallstone ileus--technical report and review of the literature. *J Laparoendosc Adv Surg Tech A* 2012; **22**: 265-268 [PMID: 22303929 DOI: 10.1089/lap.2011.0375]

33 **Bircan HY**, Koc B, Ozcelik U, Kemik O, Demirag A. Laparoscopic treatment of gallstone ileus. *Clin Med Insights Case Rep* 2014; **7**: 75-77 [PMID: 25187746 DOI: 10.4137/CCRep.S16512]

34 **Shiwani MH**, Ullah Q. Laparoscopic enterolithotomy is a valid option to treat gallstone ileus. *JSLS* 2010; **14**: 282-285 [PMID: 20932386 DOI: 10.4293/108680810X12785289144764]

35 **El-Dhuwaib Y**, Ammori BJ. Staged and complete laparoscopic management of cholelithiasis in a patient with gallstone ileus and bile duct calculi. *Surg Endosc* 2003; **17**: 988-989 [PMID: 12632139 DOI: 10.1007/s00464-002-4275-5]

36 **Doko M**, Zovak M, Kopljar M, Glavan E, Ljubicic N, Hochstädter H. Comparison of surgical treatments of gallstone ileus: preliminary report. *World J Surg* 2003; **27**: 400-404 [PMID: 12658481 DOI: 10.1007/s00268-002-6569-0]

37 **Tan YM**, Wong WK, Ooi LL. A comparison of two surgical strategies for the emergency treatment of gallstone ileus. *Singapore Med J* 2004; **45**: 69-72 [PMID: 14985844]

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CASE REPORT

Treatment options for spontaneous and postoperative sclerosing mesenteritis

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Abstract

Sclerosing mesenteritis is a rare pathology with only a few described cases in the literature. The etiology is unclear; however, several potential triggers, including abdominal surgery and abdominal trauma, have been discussed. The pathology includes a benign acute or chronic inflammatory process affecting the adipose tissue of the mesenterium. Despite it being a rare disease, sclerosing mesenteritis is an important differential diagnosis in patients after abdominal surgery or patients presenting spontaneously with signs of acute inflammation and abdominal pain. We present here three cases with sclerosing mesenteritis. In two cases, sclerosing mesenteritis occurred postoperatively after abdominal surgery. One patient was treated because of abdominal pain and specific radiological signs revealing spontaneous manifestation of sclerosing mesenteritis. So far there are no distinct treatment algorithms, so the patients were treated differently, including steroids, antibiotics and watchful waiting. In addition, we reviewed the current literature on treatment options for this rare disease.

Key words: Sclerosing mesenteritis; Abdominal pain; Inflammation; Surgery; Immunosuppression

Core tip: Sclerosing mesenteritis is a rare pathology including a benign acute or chronic inflammatory process affecting the adipose tissue of the mesenterium. The etiology is unclear; however, several potential triggers, including abdominal surgery and abdominal trauma, have been discussed. So far there is no evidence in the treatment of these patients. But, in the case of a non-resolving bowel obstruction, surgery is needed.

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INTRODUCTION

Sclerosing mesenteritis is a rare, benign pathology of the abdominal adipose tissue[1]. It was first described by Jura[2] in 1924. Sclerosing mesenteritis, mesenteric or omental panniculitis, mesenteric lipodystrophy, or mesenteric manifestation of Weber-Christian disease are often used as synonymous terms[1,3]. The etiology is unclear and often remains idiopathic, but abdominal surgical procedures, abdominal trauma, infections, autoimmune processes, drugs, vasculitis, avitaminosis and hypersensitivity have been discussed as potential triggers[1,3,4]. The symptoms of sclerosing mesenteritis are mostly unspecific. Hence, it is crucial to rule out other pathologies such as lymphoma, sarcoma, peritoneal mesothelioma, infectious diseases (tuberculosis or histoplasmosis) or amyloidosis[3].

The objective of these case presentations and the summary of the literature is to raise awareness regarding this rare, yet important, differential diagnosis in a patient presenting with signs of acute inflammation and abdominal pain. Furthermore, the current literature regarding possible treatment regimens will be discussed.

CASE REPORT

Case 1

A 64 years old male patient with attenuated familial polyposis coli was electively admitted for laparoscopic subtotal colectomy. His previous surgical history consisted of inguinal hernia repair. Comorbidities included coronary artery disease, status post percutaneous transluminal coronary angiography and stenting two years earlier. Laparoscopic subtotal colectomy, including an ileo-rectal anastomosis and preservation of the greater omentum, was performed without any intraoperative complications. After an uneventful initial course, the patient developed symptoms of incomplete intestinal obstruction with vomiting and diarrhea on the third postoperative day. Moreover, the temperature rose to 101.3 degrees Fahrenheit. On clinical examination, the patient was very tender over his left hemiabdomen. The blood work revealed a dramatic elevation of the C-reactive protein (CRP) to 478 mg/L (normal: Less than 3 mg/L) and a white blood cell count of 16.1 G/l (normal: Less than 10.0 G/L). An abdominal computed tomography (CT) showed an unclear mass of 15 cm × 8.8 cm × 7.8 cm in the left hemiabdomen (Figures 1 and 2), consisting of omental fat and causing a partial intestinal obstruction. After administration of intravenous antibiotics (tazobactum/piperacillinum) and conservative treatment of the bowel obstruction with insertion of a naso-gastric tube and rectal catheter, the patient's general condition improved and the bowel function normalized over the following days. The abdominal tenderness disappeared and the blood values returned to within normal limits. The patient was discharged with oral antibiotics (amoxicillinum/acidum clavulanicum) on postoperative day 20 in good general condition. The patient, who was seen in the outpatient

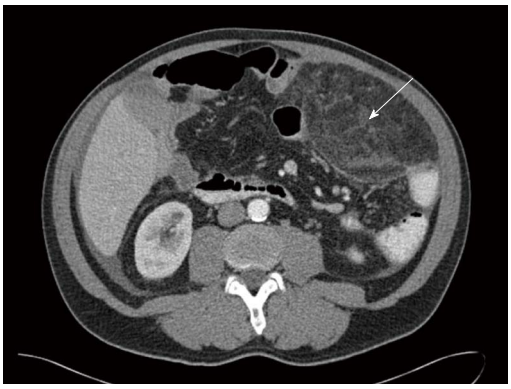

Figure 1 Transverse abdominal computed tomography scan with a tumor mass (15 cm × 8.8 cm × 7.8 cm, white arrow) in the upper left hemiabdomen. The mass shows increased density in comparison to normal fat and a tumoral pseudocapsule.

Figure 2 Sagittal abdominal computed tomography scan with an unclear mass in the omental fat with obstruction of the small intestine (white arrow).

Figure 3 Transverse abdominal computed tomography scan as the gold standard with an inflammation of the mesenterium at the height of the navel.

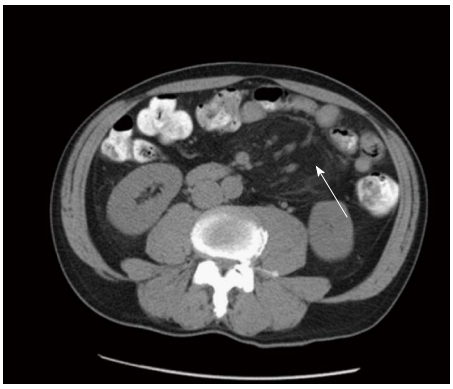

Figure 5 Inflammation of the small bowel adipose tissue formed as a pseudotumor in the left abdomen in the transverse abdominal computed tomography (white arrow).

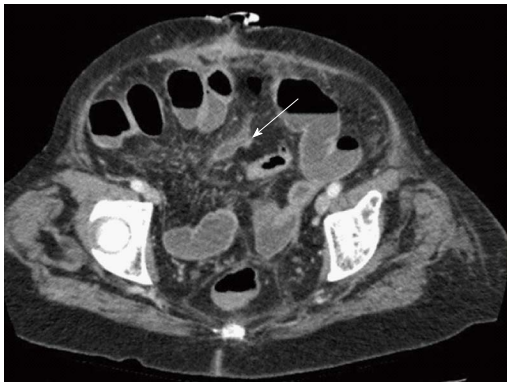

Figure 4 Transverse abdominal computed tomography scan shows a nonspecific inflammatory process involving the adipose tissue of the small bowel mesentery.

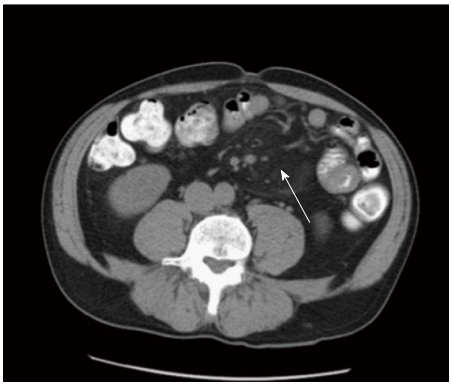

Figure 6 Signs of sclerosing mesenteritis with lymphadenopathy in the lower left abdomen in the transverse abdominal computed tomography (white arrow).

clinic 4 wk later, remained asymptomatic.

Case 2

An 84 years old female patient was referred to the hospital with upper abdominal pain associated with diarrhea and vomiting for one week. The CT scan confirmed the diagnosis of an intestinal obstruction. An explorative laparotomy with adhesiolysis and a partial resection of the small bowel with an end-end-anastomosis of the small bowel was performed because of an ischemic perforation. During the postoperative course, the patient complained of progressive and vague abdominal pain. In addition to elevated inflammatory parameters (CRP, white blood cell count), no surgical complication or infection was detected. The repeated CT scans showed signs of mesenteritis without signs of leakage or abscess (Figures 3 and 4). There was no improvement with antibiotic treatment, but empirical therapy with prednisolone reduced the pain and the inflammatory parameters decreased. In the follow-up 40 d after surgery, the patient was asymptomatic.

Case 3

A healthy 56-year old male patient presented with history of pain in the lower abdominal quadrant for 3 to 4 mo, provoked by exercise. The patient's past medical history was uneventful, with no weight loss, no episodes of fever or shivering, no evidence for dysfunction of the gastrointestinal tract, and no previous abdominal surgeries. The patient underwent a screening colonoscopy without any pathologic findings. A clinical examination revealed abdominal distention in the left lower quadrant without peritonitis or resistance. An abdominal CT scan showed an inflammatory infiltration of the mesenteric adipose tissue with lymphadenopathy, interpreted as sclerosing mesenteritis without evidence of malignancy or other pathology (Figures 5 and 6). The pain declined further in the course spontaneously without any treatment.

DISCUSSION

There are only a few described cases of sclerosing mesenteritis in the literature. The pathogenesis of sclerosing mesenteritis remains to be elucidated; however, it seems to be an inflammatory and immune response to local stimuli, such as abdominal surgery or trauma. Moreover, infections, autoimmune processes, malignancy, drugs, vasculitis, avitaminosis and hypersensitivity have been described as potential

causes for sclerosing mesenteritis[5-7]. Furthermore, immunological disorders, such as elevated IgG4 levels, have been discussed as related to the occurrence of sclerosing mesenteritis[8,9]. However, the causes for sclerosing mesenteritis often remain idiopathic[1,3,4]. Histological exams reveal a benign fibro-inflammatory process of the intra-abdominal fat, including fat necrosis, signs of chronic inflammation with lymphocytes, plasma cells, lipid-laden macrophages and fibrosis. However, no malignant cells are identified[1,4,10]. The symptoms of sclerosing mesenteritis are nonspecific and may include fever, vomiting, abdominal pain with distension, abdominal tenderness as well as intestinal obstruction[3,11,12]. Because of its nonspecific presentation, it is crucial to rule out other pathologies, such as lymphoma, sarcoma, peritoneal mesothelioma, infectious diseases (tuberculosis or histoplasmosis) or amyloidosis and post-interventional abscesses and other complications[3]. Differentiating between a "real" postoperative/post-interventional complication and a sclerosing mesenteritis may be extremely challenging. As sclerosing mesenteritis is extremely rare, it is often difficult to establish a definitive diagnosis[13]. Due to the nonspecific clinical presentation, a surgical biopsy is often performed[12]; however, it is rarely actually necessary[3]. It used to be the only method to confirm the diagnosis. Today, based on the increasing use of ultrasonography and CT scan with improved quality, the diagnosis can be established based on imaging and clinical presentation[10]. In ultrasonography the features are nonspecific, including a poorly defined hyperechoic mesenteric fat with a decreased compressibility[10]. CT scans reveal a well-defined mass of fatty tissue with increased density in comparison to normal fat or a nonspecific inflammatory process involving the adipose tissue of the mesenterium of the small bowel[10,14]. In addition, a fat-ring sign, a tumoral pseudocapsule or soft-tissue nodules may be observed[10]. Clinical manifestations are nonspecific and can consist of abdominal pain (70%), diarrhea (25%), weight loss (23%), abdominal muscle defense (50%), rebound tenderness (10%-15%), ascites/chylous (14%)[3,7] and, in rare cases, fever[15]. Most patients with sclerosing mesenteritis have an uneventful course and the symptoms resolve spontaneously[3]. Several therapeutic approaches with agents such as steroids, colchicine and azathioprine have been described with various therapeutic effects[16-18]. In cases of non-resolving bowel obstruction or an advanced inflammatory reaction, surgical resection of the inflamed fat may be necessary[1,12]. Asymptomatic sclerosing mesenteritis requires no therapy[7]. However, the symptomatic sclerosing mesenteritis must be treated surgically or with a trial of immunosuppressive medication[7].

These case presentations reflect that currently the etiology and the treatment of sclerosing mesenteritis are still not fully understood and further investigations are needed. The only evidence in the treatment of these patients is that, in the case of non-resolving bowel obstruction, surgery is needed. Because of the small number of patients suffering from sclerosing mesenteritis, prospective and randomized trials are difficult to perform. Therefore, it is still under investigation if patients need immunosuppressive agents.

COMMENTS

Case characteristics

Abdominal pain and signs of acute inflammation after abdominal surgery, with specific radiological signs in two patients and in one patient without prior surgical intervention.

Clinical diagnosis

Nonspecific with signs of acute inflammation and abdominal pain.

Differential diagnosis

Lymphoma, sarcoma, peritoneal mesothelioma, infectious diseases (tuberculosis or histoplasmosis) or amyloidosis and post-interventional abscesses.

Laboratory diagnosis

Elevated C-reactive protein levels and increased white blood count.

Treatment

Steroids, antibiotics and watchful waiting. In the case of non-resolving bowel obstruction or an advanced inflammatory reaction, surgical resection is needed.

Related reports

In the current literature, there are several case reports of mostly single cases. Data from prospective and randomized studies are lacking.

Term explanation

Sclerosing mesenteritis is a rare pathology and the etiology is unclear. Several potential triggers, including abdominal surgery and abdominal trauma, have been discussed. The pathology includes a benign acute or chronic inflammatory process affecting the adipose tissue of the mesenterium.

Experiences and lessons

This disease is rare and often misdiagnosed. Especially in the postoperative course, the occurrence of sclerosing mesenteritis is often difficult to identify. The etiology is unclear and there are currently no specific treatment algorithms. The only evidence is that in the case of non-resolving bowel obstruction or an advanced inflammatory reaction, surgical resection is needed.

Peer-review

It is a well written clinical report about the rarely occurring sclerosing mesenteritis including three cases with pictorial presentation. The information conveyed should be of help to the peers in the same field for improving their clinical practice.

REFERENCES

1 **Popkharitov AI**, Chomov GN. Mesenteric panniculitis of the sigmoid colon: a case report and review of the literature. *J Med Case Rep* 2007; **1**: 108 [PMID: 17910751 DOI: 10.1186/1752-1947-1-108]

2 **Jura V**. Sclerosing and retractile mesenteritis. *Policlinica* 1924; **31**: 575-581

3 **Issa I**, Baydoun H. Mesenteric panniculitis: various presentations and treatment regimens. *World J Gastroenterol* 2009; **15**: 3827-3830 [PMID: 19673029 DOI: 10.3748/wjg.15.3827]

4 **Hirono S**, Sakaguchi S, Iwakura S, Masaki K, Tsuhada K, Yamaue H. Idiopathic isolated omental panniculitis. *J Clin Gastroenterol* 2005; **39**: 79-80 [PMID: 15599220]

5 **van Putte-Katier N**, van Bommel EF, Elgersma OE, Hendriksz TR.

Mesenteric panniculitis: prevalence, clinicoradiological presentation and 5-year follow-up. *Br J Radiol* 2014; **87**: 20140451 [PMID: 25271412 DOI: 10.1259/bjr.20140451]
6 **Badet N**, Sailley N, Briquez C, Paquette B, Vuitton L, Delabrousse É. Mesenteric panniculitis: still an ambiguous condition. *Diagn Interv Imaging* 2015; **96**: 251-257 [PMID: 25701479 DOI: 10.1016/j.diii.2014.12.002]
7 **Forcione DG**, Lamont JT, Grover S. Sclerosing mesenteritis. 2011 UpToDate. Available from: URL: http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?5/61/6096?source=HISTORY
8 **Harvin G**, Graham A. Sclerosing Mesenteritis: A Rare Cause of Small Bowel Obstruction. *Case Rep Gastroenterol* 2016; **10**: 63-67 [PMID: 27403104 DOI: 10.1159/000444413]
9 **Chen TS**, Montgomery EA. Are tumefactive lesions classified as sclerosing mesenteritis a subset of IgG4-related sclerosing disorders? *J Clin Pathol* 2008; **61**: 1093-1097 [PMID: 18682417 DOI: 10.1136/jcp.2008.057869]
10 **van Breda Vriesman AC**, Schuttevaer HM, Coerkamp EG, Puylaert JB. Mesenteric panniculitis: US and CT features. *Eur Radiol* 2004; **14**: 2242-2248 [PMID: 15300397 DOI: 10.1007/s00330-004-2429-7]
11 **Ruiz-Tovar J**, Alonso Hernández N, Sanjuanbenito Dehesa A, Martínez Molina E. [Mesenteric paniculitis: report of ten cases]. *Rev Esp Enferm Dig* 2007; **99**: 240-241 [PMID: 17590109]
12 **Delgado Plasencia L**, Rodríguez Ballester L, López-Tomassetti Fernández EM, Hernández Morales A, Carrillo Pallarés A, Hernández Siverio N. [Mesenteric panniculitis: experience in our center]. *Rev Esp Enferm Dig* 2007; **99**: 291-297 [PMID: 17650941]
13 **Volpicelli G**, Saracco W. A case of mesenteric panniculitis: multiple involvement of the emergency department before final diagnosis and appropriate treatment. *Eur J Emerg Med* 2007; **14**: 104-105 [PMID: 17496688]
14 **Canyigit M**, Koksal A, Akgoz A, Kara T, Sarisahin M, Akhan O. Multidetector-row computed tomography findings of sclerosing mesenteritis with associated diseases and its prevalence. *Jpn J Radiol* 2011; **29**: 495-502 [PMID: 21882092 DOI: 10.1007/s11604-011-0587-5]
15 **Hirano H**, Yoshida A, Sasae Y, Sakuta T, Morita Y. Mesenteric panniculitis: a rare cause of fever. *Int J Rheum Dis* 2012; **15**: e40-e42 [PMID: 22462435 DOI: 10.1111/j.1756-185X.2011.01658.x]
16 **Miyake H**, Sano T, Kamiya J, Nagino M, Uesaka K, Yuasa N, Oda K, Nimura Y. Successful steroid therapy for postoperative mesenteric panniculitis. *Surgery* 2003; **133**: 118-119 [PMID: 12563249 DOI: 10.1067/msy.2003.54]
17 **Tytgat GN**, Roozendaal K, Winter W, Esseveld MR. Successful treatment of a patient with retractile mesenteritis with prednisone and azathioprine. *Gastroenterology* 1980; **79**: 352-356 [PMID: 7399242]
18 **Fasoulas K**, Beltsis A, Katsinelos T, Dimou E, Arvaniti M, Charsoula A, Gourvas V, Atmatzidis S, Chatzimavroudis G, Katsinelos P. Efficacy of colchicine in the treatment of mesenteric panniculitis in a young patient. *Saudi J Gastroenterol* 2012; **18**: 146-148 [PMID: 22421723]

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